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Volume 236 **JANUARY 2, 1947** **Number 1**

COARCTATION OF THE AORTA 1
Edward D. Maire

HORMONE-PRODUCING TUMOR OF ADRENAL CORTEX, WITH CONGENITAL ABSENCE OF CONTRALATERAL ADRENAL GLAND 13
Harry M. Spence and F. Gregg Thompson, Jr.

ACUTE APPENDICITIS OCCURRING DURING THE COURSE OF OTHER DISEASES . . 20
Elliott S. Hurwitt

ASIATIC SCHISTOSOMIASIS 24
Lyman O. Warren, Jr.

MEDICAL PROGRESS: THE PHYSIOLOGIC AND CLINICAL SIGNIFICANCE OF PLASMA PROTEINS AND PROTEIN METABOLITES (To be concluded) 26
Jack Metcoff and Fredrick J. Stare

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL 36

EDITORIALS
Further Reasons for the Nurse Shortage 41
Doctors East, Doctors West 41

DEPARTMENTS
Massachusetts Medical Society 42
Massachusetts Department of Public Health 42
Correspondence 43
Book Review 44
Notices 44

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Volume 236 JANUARY 2, 1947 Number 1

COARCTATION OF THE AORTA

A Review and a Report of a Case

EDWARD D. MAIRE, M.D.*

DETROIT, MICHIGAN

IN 1933 Sir Thomas Lewis[1] expressed the following opinion: "So much has been written about coarctation of the aorta that new records of cases can have little value unless they reveal new features of interest and importance to the study of the condition." With this sentence he began a paper that — for completeness in both theoretical and practical considerations, as well as in the presentation of the anatomic, physiologic and clinical features — can well be used as a model by present-day authors on any medical subject.

The purpose of this paper is to report a case of coarctation of the aorta in a bombardier, to reemphasize much of what Sir Thomas Lewis had to say about the subject, to abstract several points brought out by a few of the earlier and later writers, to emphasize the ease of diagnosis of the anomaly, to exhort physicians to search for the condition oftener, to discuss the prognosis in coarctation of the aorta, particularly as the problem pertains to civil, military and Veterans Administration practice and, what is perhaps most important, to report on the recent advances in the surgical treatment of aortic atresia.

ANATOMY

Coarctation of the aorta is generally classified into two anatomic groups, both of which are located preponderantly in the distal portions of the arch. The first form, which is generally known as the infantile type, is characterized by a generalized narrowing of the arch in its distal portion, extending from the origin of the left subclavian artery to the region of insertion of the ductus arteriosus. Clinically, this form is rare, accounting for 7 of 183 cases cited in one series,[2] and is so frequently accompanied by other major developmental anomalies, such as a bilocular or trilocular heart, a transposition of the arterial trunks and pulmonary atresia,[2] that death occurs in infancy. The adult type is characterized by an abrupt narrowing — sometimes to the extent of obliteration — of the aorta in the proximity of the insertion of the ligamentum arteriosum (Fig. 1); it should not be classed as a rarity in clinical medicine. Blackford[3] found an incidence of 44 cases in 68,300 cases at autopsy (1:1550) reported by various observers. The incidence is 3:1 in favor of men. That the patient with the adult type of coarctation lives — and, in fact, may physically prosper — for years in spite of so marked a defect is probably due to the responsiveness of other vessels in forming a collateral circulation, as well as to the fact that the associated developmental anomalies, if any, are less serious than those found in the infantile group. These defects, which are comparatively minor,[2] fall into two main groups. The first comprises anomalies of the heart and great vessels, including bicuspid aortic valve, anomalous origin of the arteries of the aortic arch, persistent left superior vena cava, aortic septal defects and subaortic stenosis, and the second, anomalies of the body at large, including hypospadias, absence of the left kidney, vertical position of the stomach, horseshoe kidney, diaphragmatic hernia, subluxation of the joints, slight Mongolianism, ichthyosis, pigeon breast and congenital cerebral-vessel aneurysm. Because of the obvious value of a search for these associated anomalies these lists are taken directly from an article by Hamilton and Abbott.[2] These authors state that the defects of the heart and great vessels are so frequent as to be almost a part of the complex. Bauer and Iverson[4] described a case accompanied by complete double pelvis and ureter and an accessory renal artery on the left. That many developmental anomalies exist in aortic coarctation may be fully expected with a defect that is probably an embryologic deviation itself.

PHYSIOLOGIC CIRCULATORY CHANGES

Marked anatomic changes of the various branches of the aorta, all designed to establish a satisfactory circulation to the organs normally supplied by

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arteries branching from the aorta distal to the coarctation, develop with the demands of the body. The formation of this collateral circulation,[2] although not uniform, takes place mainly through the intrascapular and subscapular arteries, all of which arise from branches of the aortic arch and thus proximal to the stenosis, and the second intercostal artery; blood passes through the internal mammary

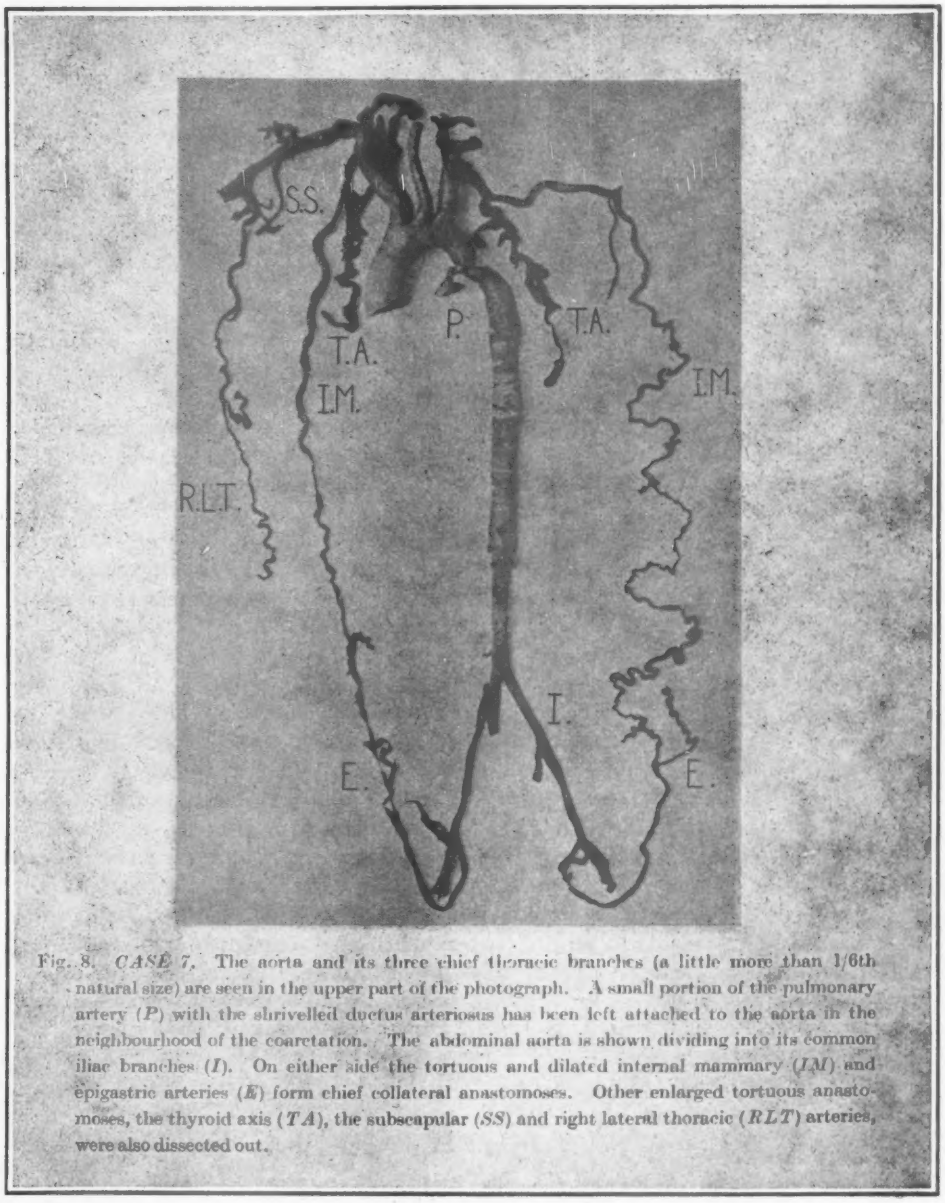

Fig. 8. *CASE 7.* The aorta and its three chief thoracic branches (a little more than 1/6th natural size) are seen in the upper part of the photograph. A small portion of the pulmonary artery (*P*) with the shrivelled ductus arteriosus has been left attached to the aorta in the neighbourhood of the coarctation. The abdominal aorta is shown dividing into its common iliac branches (*I*). On either side the tortuous and dilated internal mammary (*IM*) and epigastric arteries (*E*) form chief collateral anastomoses. Other enlarged tortuous anastomoses, the thyroid axis (*TA*), the subscapular (*SS*) and right lateral thoracic (*RLT*) arteries, were also dissected out.

FIGURE 1.

This illustration, taken from Lewis,[1] illustrates the formation of the collateral circulation.

following developments: an anastomosis between the superior intercostal artery, arising from the subclavian, and the first aortic intercostal artery, which comes from a point just distal to the stenosis; an anastomosis between the posterior scapular, branch of the subclavian to the descending aorta via the epigastric and iliac arteries (Fig. 1). This collateral circulation, when well developed, supplies sufficient blood to the aorta distal to the coarctation so that, even should obliteration be complete, cir-

culation of blood to the viscera of the abdomen and to the musculature of the lower extremities is frequently satisfactory. It has been shown that the blood vessels of the skin and muscles of the lower extremities are normal in comparison to those of the upper extremities and regions supplied by blood vessels proximal to the coarctation.[5]

The blood flow appears not to be uniformly affected, since some authors have discovered a decrease in renal flow[6] and others an increase in the peripheral vessels.[7] In a careful study of 12 cases by Stewart and his associates,[7] the circulation time was found to be prolonged in some, normal in a few and decreased in others. They point out that the prolongation of the circulation time was effected by the devious collateral routes of the blood and that the normal or decreased times were produced by a well developed increase in the cardiac output that overcame this handicap; the skin and rectal temperatures were also increased as a rule. Blumgart et al.[8] noted intermittent claudication and nocturnal cramps in the legs of 2 patients over forty years of age, and they concluded that the velocity flow in the larger arteries of the legs was reduced and the femoral pulse delayed as much as 0.15 second after the radial pulse. They found the blood oxygen in the lower extremities not diminished in a patient at rest. Stewart and Bailey[9] found the arm-to-perineum and arm-to-leg circulation times prolonged in most of 14 cases. The aorta and all the arteries arising from it proximal to the constriction undergo absolute dilatation,* and the left ventricle usually hypertrophies slightly, especially if high blood pressure be present, in well marked, uncomplicated cases of coarctation. Lewis[1] believed that this dilatation produced a volume in the arterial bed proximal to the coarctated region about equal to the arterial volume in the normal person without

FIGURE 2.

A roentgenogram, taken from Lewis,[1] illustrates sulcation of the inferior borders of the posterior portions of the ribs.

*Measurement of the degree of dilatation of the aortic branches would be tedious and technically difficult. To measure merely the mouths of the great branches at the aorta as suggested by some[4] is entirely inadequate, for the elasticity and the caliber of the lumen along the entire course of these vessels must be calculated to ascertain the complete degree of dilatation.[1]

stenosis; in other words, the increased resistance to the blood leaving the left ventricle, expected on the contraction of that organ because of aortic constriction, is compensated for by dilatation of the proximal aorta and its branches. This answers part of the query of why a heart working against an increased tension is often little enlarged but leaves unanswered the question of the cause of the hypertension.

In view of one of the modern concepts of the etiology of hypertension, reduced blood flow to the kidney, it is emphasized that the volume flow and circulation time to this organ may or may not be normal, although some believe that adverse changes have been demonstrated.[6] Using direct puncture methods for determining the blood pressures in the brachial and femoral arteries in a case of coarctation, Steele and Cohn[10] found that the systolic pressure in the brachial artery was higher but that the diastolic pressure in the femoral artery was almost the same as that in the brachial artery. This suggested that the peripheral resistance is increased in the legs as well as in the arms.

Embryology

Embryologists are probably quite close to the explanation of the development of coarctation of the adult type. Brunner[11] asserted that the tissue of the ductus arteriosus at its junction with the aorta, which at birth naturally becomes completely stenosed, anomalously incorporates the contiguous portion of the aorta in this obliterating action. The primitive fourth arch (the aorta) falls prey to the obliterating overaction of the primitive sixth arch (the ductus). Some authors point out that the ligamentum arteriosum exerts a tent-rope-like tugging on the aorta at the junction of the two, causing

Figure 3.

This roentgenogram, taken from Lewis,[1] is a left oblique view that illustrates the extension of the great-vessel silhouette high into the neck and an area of abnormal clearness posterior to the aortic column.

a kinking of the aorta that produces a stenosis. Just what the process is in the extremely rare cases of coarctation situated away from the region of the ductus insertion is difficult to conjecture. One case is cited in which the stenosis occurred proximal to the origin of the left subclavian artery,[2] and record has been made of a stenosis in the abdominal aorta.[12] Such locations lend support to the theory of Reynaud and Rokitansky, who believed that coarctation was due to embryonic maldevelopment of the descending limbs of the primitive left aorta.

FIGURE 4.

A roentgenogram, taken from Lewis,[1] showing the area of abnormal clearness posterior to the aortic column in the right oblique view.

SYMPTOMS

Although the adult type of coarctation of the aorta is present at or soon after birth (if Skoda's theory of postnatal paulocardia is correct) and persists throughout life, — whose span it definitely shortens, as pointed out below, — the symptoms are conspicuous by their absence. This is especially true, in the majority of cases, in the early decades of life — that is, until the reserve of nature's bounty is consumed. Patients rarely present complaints until early adulthood and usually reach the third and fourth decades before consulting a physician, in spite of the fact that the expectancy of life is much shortened. Abbott[13] reported that in 74 per cent of 200 cases the patients died during or before the fortieth year. Lewis's[1] report included 8 soldiers, all of whom had led vigorous lives in childhood and who had done well during rigorous training or combat in World War I. One of his patients first presenting symptoms of fatigability and breathlessness on exertion at the age of nineteen years had, in boyhood, walked several miles each day to school, performed physical drill and played with his school fellows such games as cricket, football and leapfrog

without difficulty; after returning home he had played in the streets till late, going to bed at 10 or 11 o'clock. He had frequently taken part in races of several miles' length and had held his own. For five years he had worked with a cabinetmaker, doing heavy carpentering and porterage for twelve hours a day; he had played football on Saturday afternoons and had usually walked six miles on Sundays. After three months of full military training at the age of nineteen, the patient had first noticed breathlessness and palpitation on exertion, in addition to an occasional cough and frequent giddiness. He was discharged from the Army at that time because of heart disease, but two years later he was again passed as healthy and returned to training, after which the symptoms recurred. From then on, with the history of continual reappearance of symptoms when he attempted heavy physical activity, the course was downward. At the age of thirty-one, he collapsed suddenly and died on his way to the hospital. A second soldier, who had passed his physical examination at the age of forty-six and had campaigned without symptoms in France and Macedonia for three and a half years, after contracting malaria, had developed breathlessness on effort, pain across the chest anteriorly, fatigability, giddiness and frontal headaches; semi-invalided at the age of sixty-three, he was still under treatment at the time of the report. These cases, with 6 others cited, demonstrated typical histories of early well-being, with symptoms of breathlessness and palpitation on exertion, chest pain, giddiness and cough first ushered in at an adult age by some extraordinary incident such as extreme exertion or infection. Frequently, once the symptoms have made their appearance, invalidism develops and death from cardiovascular failure ensues. In Lewis's 9 cases, 2 patients began to have symptoms as early as nineteen years of age, 1 at twenty-seven, 1 at thirty-three, 1 at forty, 1 at forty-one and 2 at forty-eight. The significant chronologic data in these cases are presented in Table 1. Death has occurred early in childhood and as late as ninety-two years of age, as in Reynaud's case, quoted by many writers.

The important symptoms, beginning after years of apparent good health, consist mainly of breathlessness and palpitation on exertion, fatigability, slight cough, sometimes giddiness with hot flushing of the face, headaches and thoracic pain. The period of latency is strongly emphasized by Abbott.[13] The patient in the case reported below was referred by a neuropsychiatrist to whom he had been sent because of nervousness; precordial pain and palpitation were also present in slight degree.

Physical Signs

No disease — certainly no congenital cardiovascular disease — furnishes such unmistakable physical signs as coarctation. Foremost of all findings is the reversed relation of the brachial and popliteal arterial blood pressures. The ordinary increase in pressure from 10 to 50 mm. of mercury at the popliteal artery is not present, and the pressure in the brachial artery is usually abnormally high, whereas the popliteal pressure is actually considerably lower.[14] The femoral pulsation is weaker, with a definite lag in its summation, and compared to the radial pulse it is slightly delayed in its travel following ventricular systole. In my opinion, comparison of the pressures in the brachial and popliteal arteries is the *sine qua non* of diagnosis, although Lewis[1] stresses inspection of the neck and thorax for enlarged arteries engaged in the collateral circulation. It may be argued that any physician can take blood pressures,* whereas many physicians, particularly in this age of gadgets, are poor observers. Although a brachial arterial hypertension for both systolic and diastolic values is the rule, the brachial pressure is occasionally normal.[14] Bauer and Iverson[4] encountered difficulty in the diagnosis of their 2 cases of moderate coarctation without signs of collateral circulation. In 1, the arterial pressure in the upper extremity was 30 mm. of mercury higher than that in the lower (the key to the diagnosis), and in the other no comparison of the two pressures was made. Both patients were in the throes of cardiovascular decompensation — a condition in which it is unreasonable to expect invariably large, pulsating collateral vessels in the neck and trunk, even if collateral vessels, which do not always form and which at autopsy in these cases were absent, are developed; the reversal of the normal relation of

Table 1. *Important Chronologic Data in Cases of Coarctation Reported by Sir Thomas Lewis.*[1]

Case No.	Age at Onset of Symptoms	Age at Diagnosis	Age During Invalidism	Remarks*
	yr.	yr.	yr.	
1	19	24	29–31	Sudden death at age of thirty-one
2	49½	50	50–	Patient still alive at age of sixty-three
3	19	35	19–	Patient still alive at age of thirty-seven
4	40	46	40–52	Death from congestive failure at age of fifty-two
5	49	58	50–61	Death from pneumonia at age of sixty-one
6	27	33	40–41	Sudden death at age of forty-one
7	33	42	42–43	Death from congestive failure at age of forty-three
8	41	49	41–49	Sudden death at age of forty-nine
9	68	—	—	Patient brought in dead, with no history available; diagnosis made at autopsy.

*Much of the lag in years between the onset of symptoms and the date of diagnosis took place while the patients were under close medical study, some were cases in Sir Thomas's own clinic. Case 3 had been seen more than once by Sir William Osler and Sir James Mackenzie, neither of whom had made the diagnosis.

*The usual blood-pressure cuff in use at present is not well designed for recording pressures in the thigh, snug fitting of the cuff being difficult, especially in obese patients. Manufacturers should produce a larger cuff for this purpose.

brachial and popliteal arterial tensions, on the other hand, still pertains.

Many other signs that are neither so frequently found nor so nearly pathognomonic include the following: left ventricular enlargement; a systolic murmur precordially and along the routes of enlarged collateral arteries such as the intercostal and the internal mammary arteries; diminished or absent pulsation of the arteries of the lower extremities; capillary pulsations in the face; increased pulsation in the episternal notch; and a tendency to a water-hammer quality of the radial pulses. Perlman[16] states that 9 of 13 patients had a basal diastolic murmur, 1 had a precordial systolic murmur and 3 had no cardiac murmur.

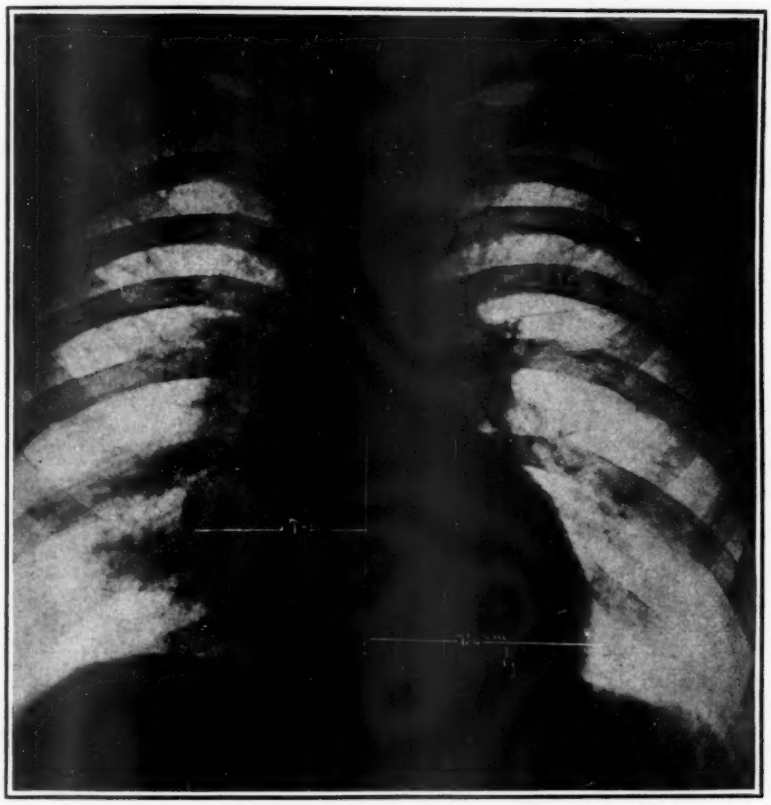

FIGURE 5.

This roentgenogram shows loss of the expected prominence of the aortic knob. Sulcation of the ribs is barely visible.

X-RAY FINDINGS

A roentgenogram of the thorax usually furnishes strong aids in the diagnosis of coarctation. The first and rather pathognomonic* finding is the scalloping of the inferior borders of the posterior ribs bilaterally, first described by Meckel[16] in 1827 and emphasized by Railsback and Dock[17] in 1929 and by others[1, 15] (see Figs. 2, 5 and 6). This phenomenon, which is found particularly in cases of long standing, is undoubtedly due to rib erosion by the forceful pulsations of the enlarged intercostal arteries. Secondly, one might expect to see variations in the silhouette of the great vessels in the upper mediastinum. Sir Thomas Lewis's description of the x-ray appearance is as follows:

> The features of the x-ray silhouette in coarctation that seem to be sufficiently constant to be regarded as significant are two in number. Firstly, there is the increased breadth and density of the shadows of the basal vessels; this is associated with their dilatation but it is not characteristic of coarctation in that it also occurs in cases of simple high tension. Secondly, there is the inability to trace out the aortic arch, a fact particularly significant when it applies to the left oblique position. It is the more noteworthy because a normally developed aorta under the strain of high internal pressure is wide and throws a dense shadow, which can usually be distinguished with ease, even after it passes into the shadow of the vertebral column. In coarctation, the aorta being untraceable, the aorta and its unusually prominent branches rise as a conspicuous column from the heart, high into the thorax and root of the neck. Behind this column at its base there is an area of abnormal clearness opposite the bodies of the 6th, 7th and 8th dorsal vertebrae.

*Rarely, other pathologic conditions may cause scalloping of the rib borders. Dr. Edwin M. Wright, of the Department of Roentgenology, University of Michigan, has recently shown me sulcation of the ribs in the x-ray film of a patient suffering from neurofibromatosis. It is conceivable that other types of neoplasm may cause somewhat similar changes.

Figures 3 and 4, taken from Lewis, and Figures 6 and 7, which demonstrate the findings in the case presented below, are illustrative. Some eager scientists prefer a more definite delineation of the great vessels by the injection of a contrast medium, such as Diodrast, into the circulation. Careful studies of this type have been reported by Blumenthal and Davis[18] and by Grishman, Steinberg and Sussman,[19] and some consider the method the only available test for certain atypical forms of coarctation.[20]

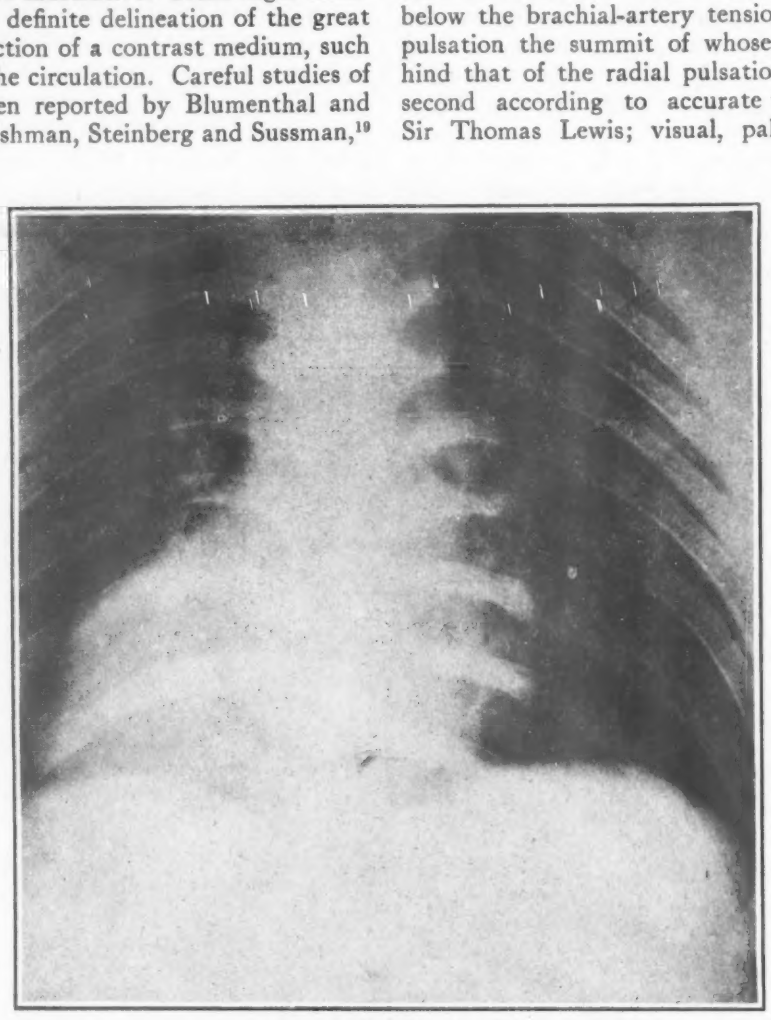

FIGURE 6.
The posteroanterior view of the posterior ribs more clearly illustrates the sulcation of the ribs.

ELECTROCARDIOGRAPHIC FINDINGS

Except for indications of a left ventricular preponderance in cases with well marked arterial hypertension, the electrocardiograph is of little value in the study of coarctation. Patients showing right-axis deviation have been reported by Stalker,[21] Moragues et al.,[22] Schwartz and Greene[23] and Stewart et al.[7] Auricular fibrillation might be expected in some patients undergoing myocardial failure,[8, 20] and right bundle-branch block has been reported.[8] Negativity and coving of T_3 occurred in 8 of 12 cases studied by Stewart et al.,[7] and these changes often indicated a poor prognosis.[9]

In summary, it can be said that the following five findings in coarctation of the aorta, when combined, are as pathognomonic as any signs in the science of diagnosis: a decrease of the arterial pressure in the lower extremities, usually to a point below the brachial-artery tension; a small femoral pulsation the summit of whose upstroke lags behind that of the radial pulsation — a lag of 0.145 second according to accurate measurements by Sir Thomas Lewis; visual, palpable or auditory evidences of increased pulsations of various arterial branches of the aorta, or a combination of two or more of these; sulcation along the inferior margin of the posterior portions of the ribs; and absence of the aortic knob and abnormal extension toward the neck of the silhouette of the supracardiac vessels.

CASE REPORT

A 26-year-old bombardier, a veteran of sixty-five "rough" missions over Germany and France during the 10 months beginning in April, 1944, noticed sharp fleeting pains across the center of the precordium in October, of that year. These pains occurred only during rest, and although palpitation and moderate breathlessness were noticed after physical exertion, there was no associated apprehension. The patient was aware of a steadily increasing incidence of the pains, as well as of a growing nervousness, but he considered both to be due to the fact that he was "crowding in as many missions as possible in order to get it over." On returning to the United States, the patient was found to have a heart murmur with high blood pressure, because of which he was removed from flying status. His current duties in the Army were light, but he continued to have precordial pains (as

many as twenty fleeting attacks a day), slight breathlessness on exertion and indefinite nervousness with irritability. During the preceding few months he had occasionally had brief spells of giddiness. Close questioning revealed no history of cough, hemoptysis, edema, cyanosis, flushing of the face, tingling or coldness of the lower extremities or indigestion. Until the onset of the present illness the patient had always been unusually strong and well.

In the family history it was stated that his father, at the age of 63, had chronic rheumatism, a brother had had inflammatory rheumatism, and another had had a questionable chorea. Perhaps relevant to the patient's condition was the fact that his mother had suffered from high blood pressure and kidney disease for years before a terminal right hemiplegia at the age of 50.*

Physical examination in April, 1945, disclosed a symmetrically developed man, 72 inches in height and 180 pounds in weight. He appeared to be especially rugged, with no apparent discomfort or pain. When a tension of 160/90 in the left and 158/80 in the right brachial arteries was observed, the right and left popliteal pressures were taken and found to be 98/78 and 98/85 respectively. No pulsations could be seen or felt over the thoracic or abdominal surfaces, but a soft, rather high-pitched murmur was distinctly heard just to the left of the 6th and 7th thoracic vertebras and along the course of the right 4th and 5th ribs posteriorly. The postmanubrial and precordial dullnesses were normal. A moderate (Grade II or III), fairly high-pitched, late systolic murmur was heard over the precordial 3rd and 4th interspaces and along the left border of the sternum. No diastolic murmur was detected. On exercise the murmurs along the right intercostal spaces became louder, whereas the murmur described in the left scapular region became inaudible when the patient stood erect but returned when he assumed a stooping position — a surprising phenomenon that occurred after some episodes of the exercise (fifty hops on each foot) but not others.† That the patient's arterial bed was elastic is demonstrated by the blood-pressure changes following exercise, the brachial-artery tension varying from 110/90 to 160/80 and the popliteal tension from 98/78 to 105/75. The femoral pulses felt weak, and the dorsalis pedis and posterior tibial arteries were not palpable at any examination.

The urine was normal, and serologic tests were negative. The electrocardiogram (Figs. 8 and 9) was entirely normal, with no evidence of axis deviation. The roentgenograms (Figs.

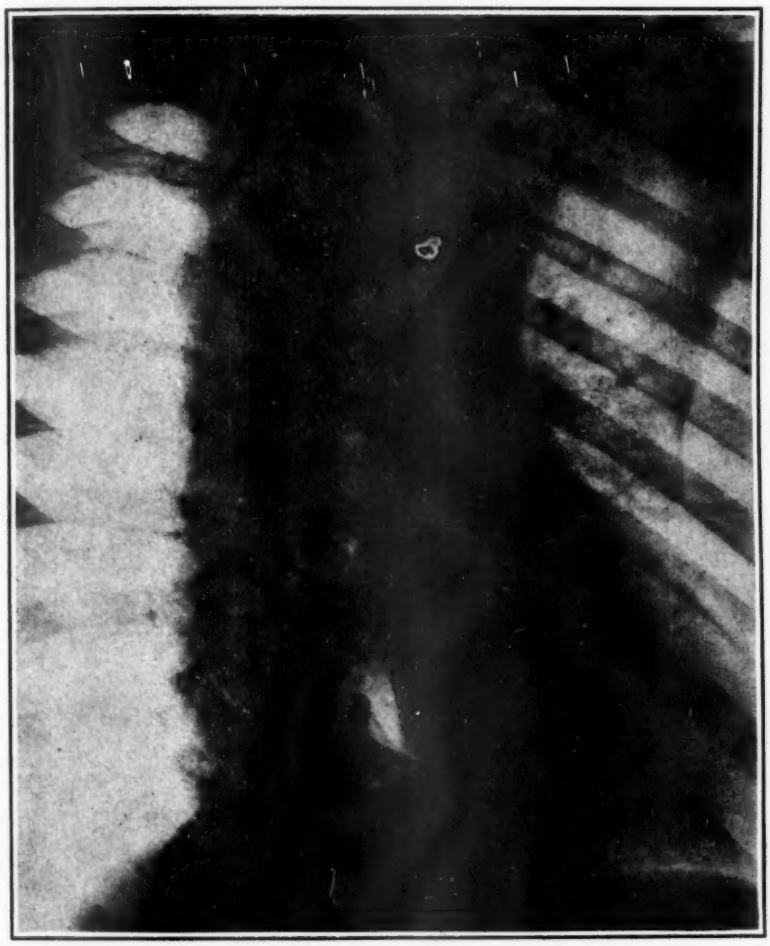

FIGURE 7.

This roentgenogram shows the clear area in the retrocardiac space in the right oblique view.

*I am not aware of any studies pertaining to possible familial aspects of coarctation except for a report of cases in a father and son, symptoms beginning in the former at the age of thirty-four and in the latter at the age of fifteen.[24]

†The systolic murmur at the coarctation is probably formed by the rush of blood from the narrow constricted passage into the larger spindle immediately distal. Perhaps the murmur was not produced in the upright position after exercise because of the increased volume of blood reaching the lower aorta through the collateral arteries, keeping the tides on either side of the stenosis "too full for sound and foam." On stooping over, the volume flow may have been impeded enough to allow the production of a murmur.

6 and 7) exhibited absence of the aortic knob in the anterior view and increased height of the great supracardiac vessels in the oblique projections, although the left oblique view was not considered satisfactory.

The patient was given a medical discharge from the Army at the time the diagnosis was first made, 7 months after the onset of symptoms. Five months later he reported that he was having many headaches and an increased fatigability. He found it difficult to do his former work.

Course and Prognosis

Sir Thomas Lewis[1] struck a hopeful note in the prognosis of coarctation, probably because the anomaly can be present long before the appearance of symptoms. It is significant, however, that 6 of the 8 patients he had seen during life were dead at the age of fifty-two, with the exception of 1 who died from pneumonia at the age of sixty-one. Two patients, thirty-seven and sixty-three years of age, were alive at the time of the report. All were symptomatic. Abbott[13] reported 128 fatal cases before the age of forty in her 200 collected cases, the main causes of death being failure of the myocardium, rupture of the aorta, mycotic endarteritis and aneurysm, frequently with an associated glomerulonephritis, and cerebral hemorrhage, probably based on congenital aneurysm of the cerebral arteries. Many observers have reported rupture of the aorta; in 1 case the rupture occurred 1 cm. distal to the aortic cusps, with emptying into the pericardium,[25] and another caused a dissecting aneurysm of the aortic arch.[26] Moragues et al.[22] cited 5 cases of rupture of the aorta distal to the atresia and reported a case of their own in which the aorta just below the coarctation had ruptured into the esophagus, causing hematemesis. Goodson[27] published a case in which the distal aorta ruptured into a bronchus, causing hemoptysis. It is difficult, at present, to be anything but pessimistic in the prognosis of coarctation of the aorta. Of course, many patients are alive and well whose cases were not reported in the literature, and there are many sufferers with undiagnosed cases; coarctation, however, is a disease of high morbidity and low longevity when once it has become symptomatic. Sooner or later, some episode of infection or unusual physical strain results in successive circulatory evils, and arteritis, aneurysms, bacterial vascular infections, myocarditis and embolization cause cardiovascular reserve to flutter; a fatal outcome subsequently follows.

Complications

The complications, all of which are cardiovascular, have been discussed above. It is interesting to note that only 1 patient is reported to have died from Bright's disease[28] — a further indication of an undisturbed blood supply to the kidneys.

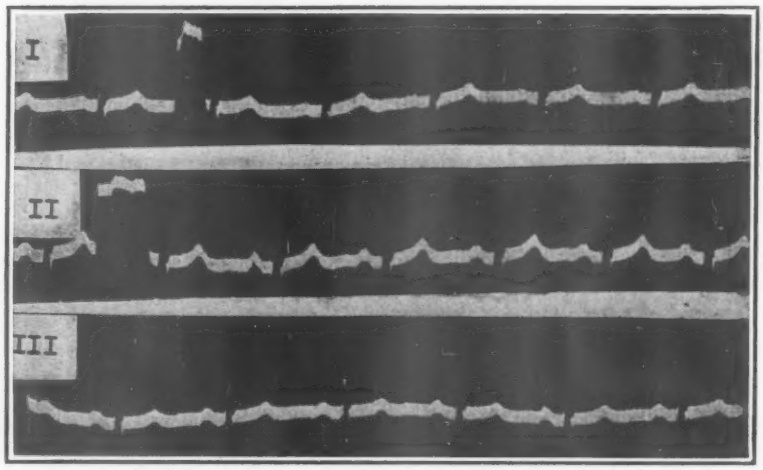

Figure 8. *Electrocardiogram — Limb Leads.*

Treatment

A simple regime of rest, both physical and mental, was the only indicated therapy until recently. If emphasis is placed on the early diagnosis of coarctation, especially before the appearance of symptoms, this form of therapy will doubtless add years to the patient's life. It behooves every examiner to keep the possibility in mind, especially in any case of arterial hypertension. A diligent examination and reappraisal of all cases of high blood pressure may prove most enlightening to the physician. Lewis,[1] investigating the effects of vasodilators on about 30 hypertensive patients in his outpatient department, discovered 5 of the 9 cases he reported. It is not too much to hope that early diagnosis and the early institution of rest, or at least protection against infections and excessive mental and physical rigors, may postpone invalidism and prolong life. Foci of infection should be carefully eliminated.

Those who discover hypertension and other cardiovascular anomalies in children may become particularly helpful in the diagnosis and treatment of coarctation of the aorta. Blumenthal and Davis[18] report the defect in a twelve-year-old child and in a twenty-month-old infant, the latter showing a blood pressure of 170 systolic, 110 diastolic, in the upper extremities but no recording being possible in the lower; in the former, a contrast medium of Diodrast was helpful in demonstrating the atresia at the insertion of the ligamentum arteriosum, as well as a dilated internal mammary artery. Schwartz and Greene[23] reported 2 cases in children — a girl of eight and a boy of nine years of age — in whom the atresia also involved the left subclavian artery so that pulsations were absent in the left arm as well as in both lower extremities. Both had an asymmetry of the upper body, with a larger face, thorax and arm on the right. The boy, who had a widely patent ductus arteriosus, exhibited no rib erosion, whereas the girl had erosion of the ribs on the right side only. The authors point out that superficial collateral circulation is rare in children. Eisenberg[29] found the diagnosis of aortic coarctation in chil-

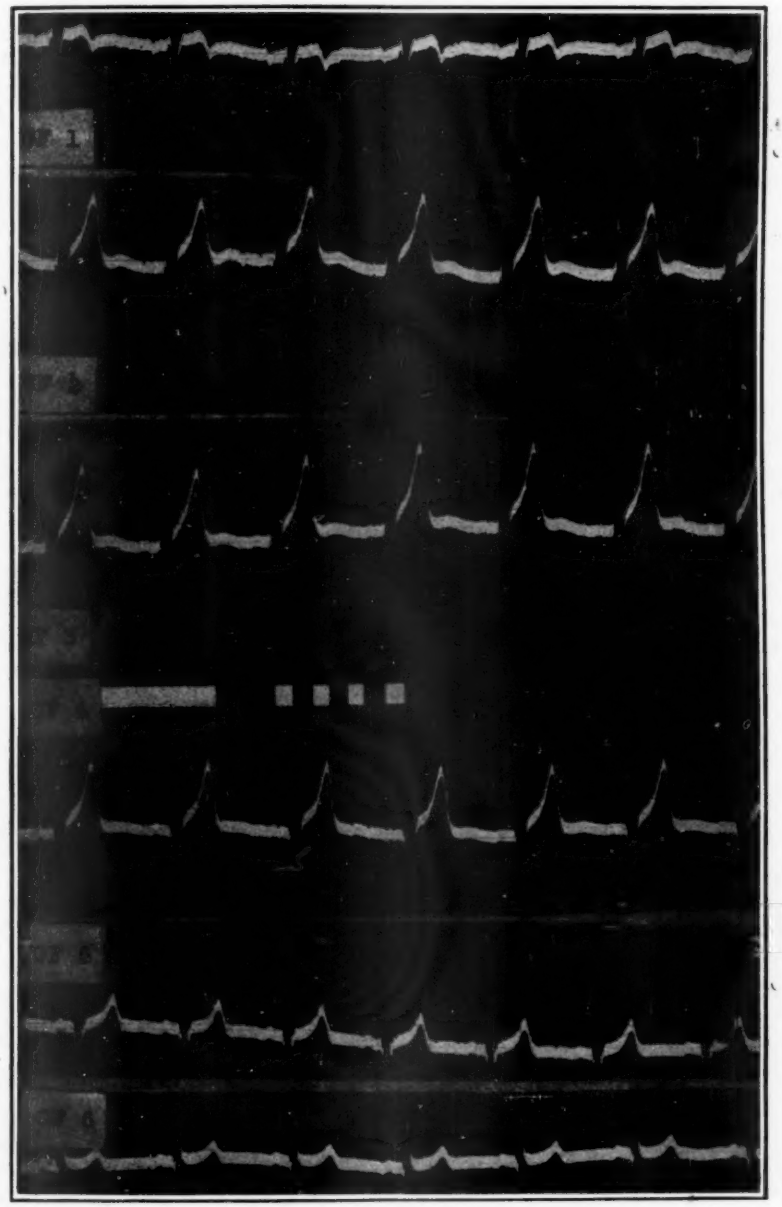

FIGURE 9. *Electrocardiogram — Precordial Leads.*

dren to be increasing. He added 3 cases in children to the literature. In 1 case the lower extremities were definitely cold to the touch, whereas in another patient, a nine-year-old child, there were a flushed face and intermittent claudication. These authors are cited to emphasize the relative frequency of the defect so that physicians may develop an awareness of it and take steps for treatment before it is too late. The remarkable advances made by the surgeon in the handling of the great blood vessels offer hope. Blalock[30] has done much to place this type of surgery on a firm foundation, and Gross and Hufnagel[31] have already cured coarctation of the aorta anatomically and clinically in a twelve-year-old child; Gross[32] reports that they have performed operations in a total of 12 cases, with success in 10. The reports of these authors should be read by all physicians, for no one can help marveling at their courage and expert technic. The surgeon may well have a cure for coarctation.

Differential Diagnosis

There is nothing typical about the patient's complaints in coarctation of the aorta. Any number of cardiovascular diseases produce the same symptoms. The signs, however, are definite and, when present in combination, are pathognomonic. The findings of a high arterial tension, with a reversal in the relation of the pressures in the brachial and popliteal arteries, and signs of a collateral circulation in the vessels of the thorax and a lag in the summation of the femoral pulse are usually distinctive and should serve to make the physician wary of the diagnosis of other forms of hypertension. The prominence of the aortic knob seen in essential hypertension is usually absent in coarctation. The x-ray film often exhibits a moderate dilatation of the ascending aorta in the uncomplicated case of coarctation, but no aneurysmal enlargement is seen. The silhouette of the dilated supracardiac vessels rises high toward the neck. If complications, such as congestive failure, aneurysms, bacterial vascular infections and embolic phenomena, occur, the picture may be confused. But the changes in the relative arterial tension, the lag of the femoral pulse summit and the x-ray findings — in the great vessels, scalloping of the ribs — should be elucidative in such cases.

* * *

Since the first case report of coarctation of the aorta by Paris[33] in 1791, the anomaly has attracted the attention of many great physicians — for example, Sir Ashley Cooper (1818), Meckel (1824), Laennec (1826), Reynaud (1828), Rokitansky (1848), Barie (1886), MacCallum (1900), Minkowski (1901), Libman (1902), Pappenheimer (1905), Mönckeberg (1907), Abbott (1928) and Sir Thomas Lewis (1933). The defect is embryologic and occurs at all ages. The symptoms, which usually do not appear before adult life, are similar to those in many types of cardiovascular failure and are not distinctive. When they once appear, the outlook is usually not bright and various degrees of invalidism are the rule. The span of life is shortened, cardiovascular complications of various types being the almost universal cause of death. The signs are definite and, when exhibited in combinations of two or three positive findings, pathognomonic. One can be sure that the defect is not rare. It has been said that coarctation occurs in about 0.10 per cent of the entire population.[34] In a routine examination of men between the ages of eighteen and thirty-five for military services, the known incidence was approximately 1:10,000.[15] In a large army general hospital, 113 of 2685 patients studied on the medical service had hypertension, and 39.7 per cent of these were under thirty years of age.[35] A search through such fields as this, including the Veterans Administration Medical Service, is bound to uncover more cases of coarctation. Since, more than ever before, cure of this disease can be hoped for, every diagnostician should make a search for it. The diagnosis is easy and interesting. Perhaps it is not too much to hope that the surgeons will be able to cure many of the patients with this disease in the not too distant future.

References

1. Lewis, T. Material relating to coarctation of aorta of adult type. *Heart* **16**:205-243, 1933.
2. Hamilton, W. F., and Abbott, M. E. Coarctation of aorta of adult type. I. Complete obliteration of descending arch at insertion of ductus in boy of fourteen; bicuspid aortic valve; impending rupture of aorta; cerebral death. II. Statistical study and historical retrospect of 200 recorded cases, with autopsy, of stenosis or obliteration of descending arch in subjects above age of two years. *Am. Heart J.* **3**:381-421, 1928.
3. Blackford, L. M. Coarctation of aorta. *Arch. Int. Med.* **41**:702-735, 1928.
4. Bauer, D. deF., and Iverson, L. Coarctation of aorta: report of two cases relating clinical data to degree of constriction measured at autopsy, with method of standardization for related measurements. *Am. Heart J.* **30**:30-38, 1945.
5. Graybiel, A., Allen, A. W., and White, P. D. Histological study of arterioles of muscle and skin from arm and leg in individuals with coarctation of aorta. *J. Clin. Investigation* **14**:52-56, 1935.
6. Friedman, M., Selzer, A., and Rosenblum, H. Renal blood flow in coarctation of aorta. *J. Clin. Investigation* **20**:107-111, 1941.
7. Stewart, H. J., Haskell, H. S., and Evans, W. F. Peripheral blood flow and other observations in coarctation of aorta. *Am. Heart J.* **28**:217-232, 1944.
8. Blumgart, H. L., Lawrence, J. S., and Ernstene, A. C. Dynamics of circulation in coarctation (stenosis of isthmus) of aorta of adult type: relation to essential hypertension. *Arch. Int. Med.* **47**:806-823, 1931.
9. Stewart, H. J., and Bailey, R. L., Jr. Cardiac output and other measurements of circulation in coarctation of aorta. *J. Clin. Investigation* **20**:145-152, 1941.
10. Steele, J. M., and Cohn, A. E. Nature of hypertension in coarctation of aorta. *J. Clin. Investigation* **17**:514, 1938.
11. Brunner, F. Ein Fall von Obliteration der Aorta an der Einmündungsstelle des Ductus Botalli. *Deutsche med. Wchnschr.* **24**:794-798, 1898.
12. Maycock, W. d'A. Congenital stenosis of abdominal aorta. *Am. Heart J.* **13**:633-646, 1937.
13. Abbott, M. E. Coarctation of aorta of adult type: statistical study and historical retrospect of 200 recorded cases with autopsy, of stenosis or obliteration of descending arch in subjects above age of two years. *Am. Heart J.* **3**:574-618, 1928.
14. King, J. T. Blood pressure in stenosis at isthmus (coarctation) of aorta: case reports. *Ann. Int. Med.* **10**:1802-1827, 1937.
15. Perlman, L. Coarctation of aorta: clinical and roentgenologic analysis of thirteen cases. *Am. Heart J.* **28**:24-38, 1944.
16. Meckel. Cited by Railsback and Dock.[17]
17. Railsback, O. C., and Dock, W. Erosion of ribs due to stenosis of isthmus (coarctation) of aorta. *Radiology* **12**:58-61, 1929.
18. Blumenthal, S., and Davis, D. B. Coarctation of aorta in childhood: report of two cases in which diagnosis was confirmed by intravenous injection of diodrast. *Am. J. Dis. Child.* **62**:1224-1232, 1941.
19. Grishman, A., Steinberg, M. F., and Sussman, M. L. Contrast roentgen visualization of coarctation of aorta. *Am. Heart J.* **21**: 365-370, 1941.
20. Grishman, A., Sussman, M. L., and Steinberg, M. F. Atypical coarctation of aorta, with absence of left radial pulse. *Am. Heart J.* **27**: 217-234, 1944.
21. Stalker, H. J. Coarctation of aorta: case with right axis deviation of electrocardiogram and auricular fibrillation with some statistics. *J. Michigan M. Soc.* **41**:40-43, 1942.

22. Moragues, V., Moore, L. T., and Rosen, J. A. Coarctation of aorta, with rupture of wall below point of constriction: report of case and review of literature. *Am. Heart J.* **24**:828-834, 1942.
23. Schwartz, S. P., and Greene, D. Coarctation of aorta in children: syndrome of constriction of isthmus of aorta, with involvement of origin of left subclavian artery. *Am. Heart J.* **23**:99-113, 1942.
24. Walker, W. G. Coarctation of aorta in father and son. *New Eng. J. Med.* **211**:1192-1195, 1934.
25. Regester, R. P., and Innes, M. B. Spontaneous rupture of aorta with hemopericardium caused by coarctation. *Am. Heart J.* **15**:365-369, 1938.
26. Lewis, R. B. Coarctation of aorta with congenital bicuspid aortic valve and dissecting aneurysm of arch of aorta. *Am. J. Clin. Path.* **15**:297-301, 1945.
27. Goodson, W. H., Jr. Coarctation of aorta: report of two unusual cases. *New Eng. J. Med.* **216**:339-345, 1937.
28. Rosenstein. Cited by Abbott.[13]
29. Eisenberg, G. Recognition of coarctation of aorta (adult type) during childhood. *J. Pediat.* **13**:303-308, 1938.
30. Blalock, A., and Park, E. A. Surgical treatment of experimental coarctation (atresia) of aorta. *Ann. Surg.* **119**:445-458, 1944.
31. Gross, R. E., and Hufnagel, C. A. Coarctation of aorta: experimental studies regarding its surgical correction. *New Eng. J. Med.* **233**: 287-293, 1945.
32. Gross, R. E. Personal communication.
33. Paris, M. Cited by Abbott.[13]
34. Levine, S. Cited by Perlman.[15]
35. McFarland, M. D. Hypertension in Army general hospital. *Mil. Surgeon* **97**:209-215, 1945.

HORMONE-PRODUCING TUMOR OF ADRENAL CORTEX, WITH CONGENITAL ABSENCE OF CONTRALATERAL ADRENAL GLAND

Report of a Case

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ALTHOUGH hyperfunctioning tumors of the adrenal cortex are rare, they are the subject of an increasing number of reports in the current literature owing both to improved diagnostic procedures, such as perirenal air insufflation and assay of the sex hormones excreted in the urine, and to increasing knowledge of the physiology of the adrenal cortex, especially in its interlocking relation with the function of the pituitary gland and the gonads.

The purpose of this communication is to present a case of a hormone-producing tumor of the adrenal cortex characterized by the symptomatology of Cushing's syndrome and associated with complete absence of the opposite adrenal gland. In addition, the recent literature on such tumors is briefly reviewed. Grollman[1] presented an exhaustive review of the literature of adrenal physiology and pathology up to 1936.

CLASSIFICATION OF ADRENAL TUMORS

In classifying adrenal tumors it must be borne in mind that the human adrenal gland is actually two glands fused together in development in one enveloping capsule. The medullary portion is derived from the neural crest of the ectodermal germ layer, and tumors of the medulla are therefore classified according to the sympathetic-nervous-system cell type from which they originate into the following groups: sympathoblastoma (from the basic nerve cells); ganglioneuroma (from the cells of the sympathetic ganglion); and pheocytoma or paraganglioma (from the pheocytes). The first two types occur primarily in children, and the last occurs chiefly in adults and is characterized by hypertensive crises.

Tumors derived from the adrenal cortex, on the other hand, are mesodermal, glandular tumors that may be cytologically divided into hyperplasias, adenomas and carcinomas. Cahill,[2-5] who has written extensively on the subject, offers the following clinical classification: those with no recognizable hormonal changes; those with changes due to excess androgens that cause adult masculinity in the female child, masculinity in the female adult and adult masculinity in the male child; those with changes due to excess estrogens causing femininity in the adult male; those with changes due to excess androgens and other steroids and exemplified by Cushing's syndrome with associated sexual changes in the male and the female; and those with changes due to excess of other steroids related to metabolism, which produce Cushing's syndrome without sexual changes in the male and the female.

The changes in the female child with a masculinizing tumor of the adrenal cortex have been described as pseudohermaphroditism. The first successful operation for a hormone-secreting adrenal tumor in a child was performed in a case of this type in an eighteen-month-old girl with virilizing symptoms reported by Collett[6] in 1924. Several additional successful cases have been reported, as well as a number of deaths. It has been noted in the latter group that associated metabolic changes were usually present and that acute adrenal insufficiency was a factor in the fatal outcome.

The term "adrenocorticogenital syndrome" or "adrenal virilism" has been applied to the occurrence of masculinizing symptoms in adult women. This condition is characterized by hirsutism, amenorrhea, atrophy of the breasts, enlargement of the clitoris and male habitus. Cahill emphasizes that of several hundred cases of virilism investigated at his clinic, only a comparatively small proportion were found to have actual tumors of the adrenal cortex.

Masculinizing tumors in immature males are rare. They result in precocious puberty, with its associated bodily changes. The so-called "infant Hercules"

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type belongs in this category, although such cases have also been reported without adrenal tumors.

Feminizing tumors in the adult male are also quite rare. Simpson and Joll[7] reported the sixth such case in 1938. In their case excessive estrogenic substance, which had been excreted in the urine preoperatively, disappeared after successful operation and reappeared when metastatic recurrence became evident.

The group of cases with symptoms due to excess androgens and other steroids is exemplified by cases of Cushing's syndrome with associated sexual changes. This combination occurs principally in adult females, although an increasing number are being reported in children, and accounts for the largest number of tumors of the adrenal cortex, although it is not confined to tumor cases.

Cushing's syndrome without sexual changes, which is due to excess production of sterols related to metabolism alone, is discussed below.

It is thus seen that the clinical picture produced by a tumor of the adrenal cortex depends on the sex and age of the patient at onset and on the varying combinations of androgenic, estrogenic and metabolic hormones secreted. Cahill[2-5] points out that the excess production of the metabolic hormones causes the functional or actual atrophy of the opposite gland. On the contrary, excess production of the androgenic hormones alone does not cause depression of the production of the life-maintaining substances by the opposite gland. This is of great importance in the prognosis following surgical extirpation of tumors of the adrenal cortex.

Relation of Cushing's Syndrome to Adrenocortical Tumors

In 1932 Cushing[8] described a syndrome, which has since borne his name, characterized by rapidly developing obesity confined to the face, neck and trunk (so-called "buffalo obesity"), plethora of the face, purplish striae over the lower abdomen and thighs, acne, amenorrhea and hirsutism in the female and impairment of sexual powers in the male. In addition, hypertension, frank or latent diabetes, disturbance of the nitrogenous metabolism and osteoporosis are frequently present. Furthermore, although not necessarily a part of the syndrome, virilism in women, as evidenced by masculine voice, atrophy of the breasts and hypertrophy of the clitoris, is often present. Cushing's syndrome occurs oftenest in adult women, next in frequency in children and less often in men.

Cushing attributed the syndrome to excessive secretion from a basophilic adenoma or hyperplasia of the basophilic cells of the anterior portion of the pituitary gland. Subsequently, as numerous cases of the syndrome appeared in the literature, it became apparent that the symptoms of many, if not a majority, were due not to primary pituitary disease but to hormone-secreting tumors of the adrenal cortex, whereas in a few cases thymic tumors or arrhenoblastomas of the ovary were found to be the principal pathologic lesions. In a considerable number of autopsied cases of Cushing's syndrome no pituitary basophilism was found, and in other series of routine post-mortem examinations basophilic adenomas were found, frequently with no clinical findings referable to them.[9-13]

It may be concluded, then, that the prevailing opinion at present is that the likeliest finding in a patient exhibiting Cushing's syndrome is a tumor of the adrenal cortex. This is particularly true in cases in which sexual changes accompany the syndrome proper.

The importance to the surgeon of the relation between Cushing's syndrome and tumors of the adrenal cortex, apart from the necessity of investigating the adrenal glands in all cases of the syndrome, lies in the fact that the prognosis for recovery after operative removal of such a tumor associated with Cushing's syndrome is much poorer than when symptoms of virilism alone are present. Thus, Thompson and Eisenhardt[12] found that in 22 surgical cases of adrenal tumor with Cushing's syndrome, 18 patients died of shock resembling adrenal insufficiency in the immediate postoperative period, whereas in cases of true virilism operative recovery is the rule. Cahill[2-5] also notes that shock from adrenal insufficiency does not occur after the removal of nonhormonal tumors of the gland or in the cases marked by sex-hormone changes only. Although recognizing that patients with Cushing's syndrome have recovered after surgical removal of an adrenal tumor, Cahill points out that unrecognized metastases are often present, and he suggests that this fact may influence the immediate recovery. Undoubtedly, the explanation of the uniform picture of postoperative acute adrenal insufficiency lies in the functional or actual atrophy of the gland on the opposite side.

Diagnosis

The diagnosis of a hormone-producing tumor of the adrenal cortex is made on the clinical examination of the patient, pertinent laboratory data and roentgenographic findings. Often, however, the diagnosis can be confirmed only by surgical exploration or autopsy.

Clinical Data

As emphasized by Cahill, the appearance of sexual precocity before puberty, pseudohermaphroditism in girls, heterosexual changes in adults and the development of Cushing's syndrome in either male or female, child or adult, are indicative of pathologic adrenal physiology, and determined effort must be made to prove or exclude the existence of the tumor in such cases.

When the tumor is suspected, the most important physical finding is a palpable mass in the region of the adrenal glands.

Laboratory Data

The laboratory tests indicated in addition to the routine blood counts and urinalysis are the blood chemical determinations of the nonprotein nitrogen, cholesterol and chloride, the glucose-tolerance curve and the assay of the excess urinary excretion of the male and female sex hormones. The latter tests are becoming increasingly important.

Lukens[14] states that thirty separate chemical substances with the sterol nucleus having hormonal effects have been isolated from the adrenal cortex. These include regulators of water and salt distribution and excretion, carbohydrate, fat and protein metabolism, growth factors and sex development. The masculinizing sex hormones have been identified as 17-ketosteroids. These may be estimated colorimetrically. The feminizing hormones are similar to the estrogens.[4]

By biologic assay, Frank[15] found that 7 out of 8 patients with adrenal carcinoma had elevated urinary estrogen excretion with a negative pregnancy test, and he concluded that the elevated estrogen finding was of value in differentiating a malignant growth from an adenoma. Wilhelm and Gross[16] reported a case of Cushing's syndrome due to a large adrenal adenoma in which the urinary androgens were markedly elevated, with a normal estrogen level. Reilly[17] has also reported a case in a six-and-a-half-year-old boy with sexual precocity due to an adrenal adenoma in whom the androgen excretion was that of an adult male, whereas the estrogen excretion was not elevated. In 2 cases of carcinoma of the adrenal gland in women — one of whom exhibited virilism and the other a Cushing's syndrome — Oppenheimer and Silver[18] found the urinary estrogens markedly elevated. The feminizing tumor in an adult male case of Simpson and Joll,[7] which showed an increase of estrogen excretion, was mentioned above. Marked elevation of both androgen and estrogen urinary excretion has been reported by Gross[19] in the case of a three-and-a-half-year-old girl who showed a masculine habitus, and enlarged clitoris and pubic hair due to an adrenal carcinoma. On the other hand, cases with hormonal changes have been described in which the excretion of the urinary sex hormone has been normal, as in the case reported by Cahill of a Cushing's syndrome due to adrenal tumor with no sex changes except amenorrhea.

Since the clinical differentiation between tumor of the adrenal cortex and cortical hyperplasia is difficult, owing to the fact that both lesions may present the same symptom complex, Talbot, Butler and Berman[20] have developed a method to distinguish between the two by fractional analysis of the 17-ketosteroids.

In summary, it may be stated that the demonstration of an elevated urinary excretion of androgenic and estrogenic substances is of value in the diagnosis of an adrenal tumor if positive but that a tumor may be present with a negative test. More research and wider usage of these tests are necessary to establish their final clinical value.

X-ray Data

An adrenal tumor often shows up as a soft-tissue shadow in the plain roentgenogram. Another frequent and valuable finding is downward displacement of the kidney in the pyelogram.

The x-ray diagnosis of adrenal tumors has been amplified by visualization of the adrenal glands by perirenal insufflation of air or oxygen. This procedure has been popularized in this country by Cahill,[2–5] who has done several hundred injections without significant untoward reaction. In essence, the procedure consists in the injection of air into the perirenal tissues, with subsequent exposure of films at intervals of from six to thirty-six hours to bring out the adrenal contour by contrast. Fish[21] reported 2 fatal cases from air embolism in approximately two hundred injections, and he recommends oxygen as preferable to air. Cope and Schatzki[22] advocate a modified technic in which 200 cc. of air is injected into the triangular fat pad below the kidney and report no complications in one hundred and sixty-three injections. Roome[23] advocates perirenal insufflation as preferable to surgical exploration when a tumor is suspected. Hyman and Wilhelm,[24] on the other hand, believe that the information gained from perirenal insufflation is of limited value and that the method should be used only as a last resort on account of its dangers.

The use of pneumoperitoneum in the following case was of definite value, although not diagnostic.

Case Report

G. E. B. (60,316), a 24-year-old married woman, was admitted to the Dependents' Ward, United States Naval Hospital, Corpus Christi, Texas, on March 29, 1945, complaining of a tumor in the abdomen of 2 months' duration. The patient stated that she had always been well until she injured her back in 1942, while riding a roller coaster. Following this injury she was in a body cast for 10 weeks. After the accident, she failed to regain strength and had frequent episodes of nausea and vomiting. One year before admission an increased growth of hair on the face had prompted her to shave her face on several occasions. She had also noted an excessive growth of hair on the arms and legs. There had been a complete amenorrhea for 2 years prior to admission. This had been attributed to hypothyroidism, for which she had received thyroid therapy without improvement. She had been married 1 year before admission, and the libido was stated to be normal. No pregnancy occurred despite the fact that contraceptives were not used. Excessive dryness of the skin, puffiness of the face and increased fat deposits about the shoulder girdle, with no change in the body weight, had been noted for several months.

Six months before admission, the patient had a sudden hemoptysis, which was found to be tuberculous in origin. She was treated with bed rest and artificial pneumothorax at a state tuberculosis sanatorium. While under treatment for pulmonary tuberculosis, she developed pain in the left upper quadrant of the abdomen and a palpable mass led to admission to this hospital. There were no symptoms referable to the urinary tract.

The past and family histories were irrelevant except as stated above.

Physical examination revealed a fairly well developed and well nourished woman with a general appearance suggestive of Cushing's syndrome. The height was 63 inches, and the weight was 106 pounds. The skin was abnormally dry, with mild acne on the face. There was a "buffalo type" of obesity involving the neck and shoulder girdle. The face was puffy, and there was an excessive amount of male type of hair on the cheeks, upper lip and chin. There was no adenopathy of the neck, and the thyroid gland was normal to palpation. The breasts were somewhat atrophic. The thorax was normal in contour. Examination of the chest showed the left lung to be clear, with physical signs of pneumothorax on the right. The heart was normal. The blood pressure varied between 140/120 and 128/116. There were striae over the lower abdomen. The pubic hair line was of masculine distribution, sulfonephthalein test showed normal renal function in both kidneys.

X-ray examination of the chest revealed the heart and great vessels within normal limits. The left lung field was clear. There was a partial pneumothorax on the right side. In the apex of the collapsed lungs there was an area of increased density interpreted as an old tuberculous lesion. A plain film showed a large oval shadow measuring 14 by 11 cm. lying just to the left of the 12th dorsal and 1st, 2nd and 3rd lumbar vertebras, overlapping the lower two thirds of the kidney shadow. There was a 2-cm. linear calcified shadow along its outer margin. Retrograde pyelograms revealed a normal kidney and ureter on the right. On the left, in addition to the mass, there was a slight hydronephrosis and hydroureter, apparently unrelated to the mass (Fig. 1).

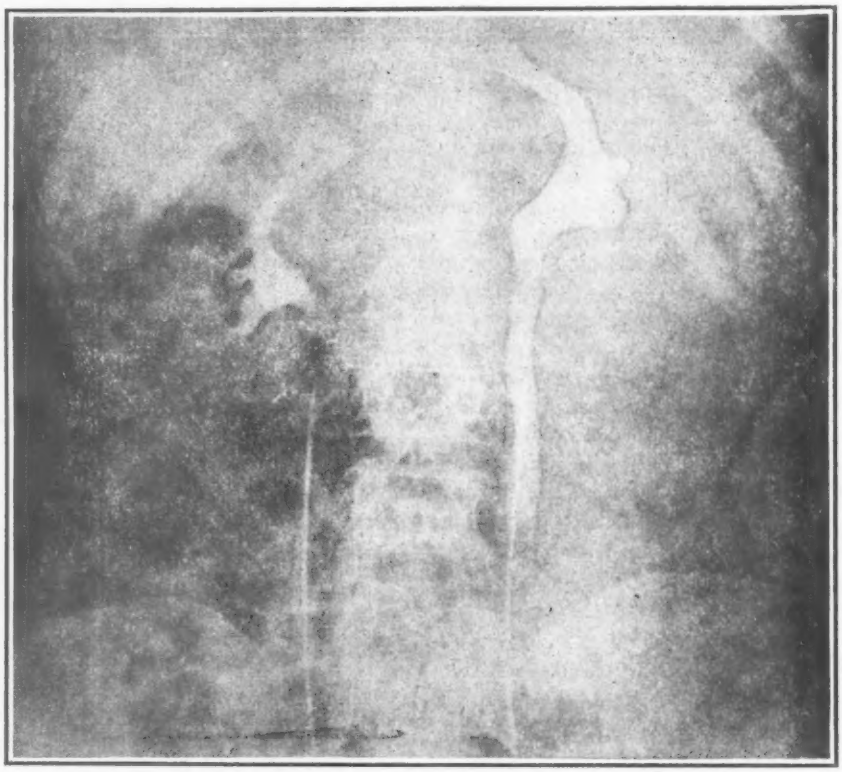

FIGURE 1. *Retrograde Pyelogram Showing Mass on the Left Side.*

extending toward the umbilicus. There was a palpable, tender, round tumor in the left upper quadrant, extending into the left flank. It was movable and descended with inspiration. There was no fixation to the abdominal wall. The tumor measured approximately 10 by 15 cm.

The external genitalia were normal, with no hypertrophy of the clitoris. Pelvic examination revealed an infantile uterus with no masses in the adnexal regions. The extremities appeared slender in proportion to the trunk. There was an excessive growth of fine hair on the arms and legs.

Examination of the blood disclosed a red-cell count of 5,100,000, with a hemoglobin of 15 gm., and a white-cell count of 10,000, with a normal differential. The fasting blood sugar was 80 mg., the blood cholesterol 140 mg. and the nonprotein nitrogen 28 mg. per 100 cc. The blood Kahn reaction was negative. The urine was normal. The sedimentation rate was 21 mm. in 1 hour.

Cystoscopic examination showed a normal bladder, with no obstruction to passage of ureteral catheters on either side; specimens obtained from each kidney were normal on microscopic examination and were sterile on culture. A phenol-

There was no evidence of distortion or displacement of the kidney by the tumor. Stereoscopic views localized the tumor anterior to the kidney and posterior to the transverse colon. A pneumoperitoneum was performed, and films in several planes confirmed the location of the tumor as shown in previous films.

The preoperative diagnosis was Cushing's syndrome due to adrenal tumor. The pulmonary tuberculosis was considered to be coincidental and, since the process was controlled, not to contraindicate surgery.

On April 13 the patient was operated on under spinal anesthesia. A transverse incision was made from the outer border of the left rectus muscle extending laterally approximately 15 cm. The incision was deepened to the perirenal space, and the kidney was explored and found to be normal. Further exploration of the wound anteriorly and extraperitoneally revealed a soft, encapsulated, ovoid tumor, the size of a grapefruit, with a vascular pedicle on its upper medial aspect.

The tumor was mobilized from a few light surrounding adhesions, and the pedicle was clamped, cut and ligated. A

search for the left adrenal gland failed to disclose any semblance of adrenal tissue. The wound was closed in layers with a cigarette drain.

The pathological report, by Dr. H. B. Williford, was as follows:

Grossly the specimen consists of a large, oval encapsulated, soft tumor measuring 13 by 9 cm. On section the tumor tissue is golden yellow, edematous and supported by a fibrous reticulum (Fig. 2).

On microscopic examination the tumor cells are arranged in small groups separated by fine connective-tissue strands (Fig. 3). No lumens are present. The cell nuclei are hyperchromatic to pale and vary in size. Most of the tumor cells show a cystoplasm of granular, foamy texture and stain a faint pink. Vascularity is generally good but becomes sparse centrally. There is no true degeneration. Along many of the blood-vessel spaces, large granular and fatty-appearing cells are present. A few giant cells are noted, with large granular nuclei or multiple nuclei. This is considered to be an adrenal tumor of the zona glomerulosa type.

Diagnosis. Malignant adenoma of the adrenal cortex.

The postoperative course for the first 24 hours was uneventful. There was no evidence of shock. The temperature was 99.8°F., the pulse 105, and the respirations 20. The blood pressure was 132/98. At the end of 36 hours, however, the patient's condition began to change for the worse. The pulse rose to 160, and the temperature began to climb rapidly, reaching 106°F. before death. The respirations rose to 30 and became shallow. The patient's color was ashen. The blood pressure became imperceptible, and she relapsed into a semicomatose state. Supportive treatment, which was started immediately after the patient began to show signs of collapse, included 100 per cent oxygen in a tent, transfusions of plasma, glucose and saline and intramuscular injections of desoxycorticosterone. The patient showed a transitory response and regained consciousness temporarily after each injection of the hormone. Despite the supportive treatment, however, she gradually became weaker and expired 48 hours after operation.

Autopsy. At post-mortem examination, which excluded the head and was done 2 hours after death, the external appearance was the same as that on physical examination. There were nodules of active tuberculosis in the apex of both lungs; the right lung was partially collapsed. The operative incision was clean, as was the site from which the tumor had been removed. All ligatures were intact, and there was no evidence of hemorrhage. No sign of adrenal tissue remained on the left. The uterus and ovaries were infantile in character, with no corpora lutea. The most striking finding was the complete absence of the right adrenal gland. Prolonged systematic search of the retroperitoneal tissues and the abdominal contents showed no vestige of adrenal tissue, and no adrenal blood supply could be identified. There was no evidence of tuberculous involvement of these tissues. It was the opinion of the pathologist, as well as of all present at the autopsy, that this case represented a congenital aplasia of the right adrenal gland and that at the time of death there was no adrenal tissue in the body.

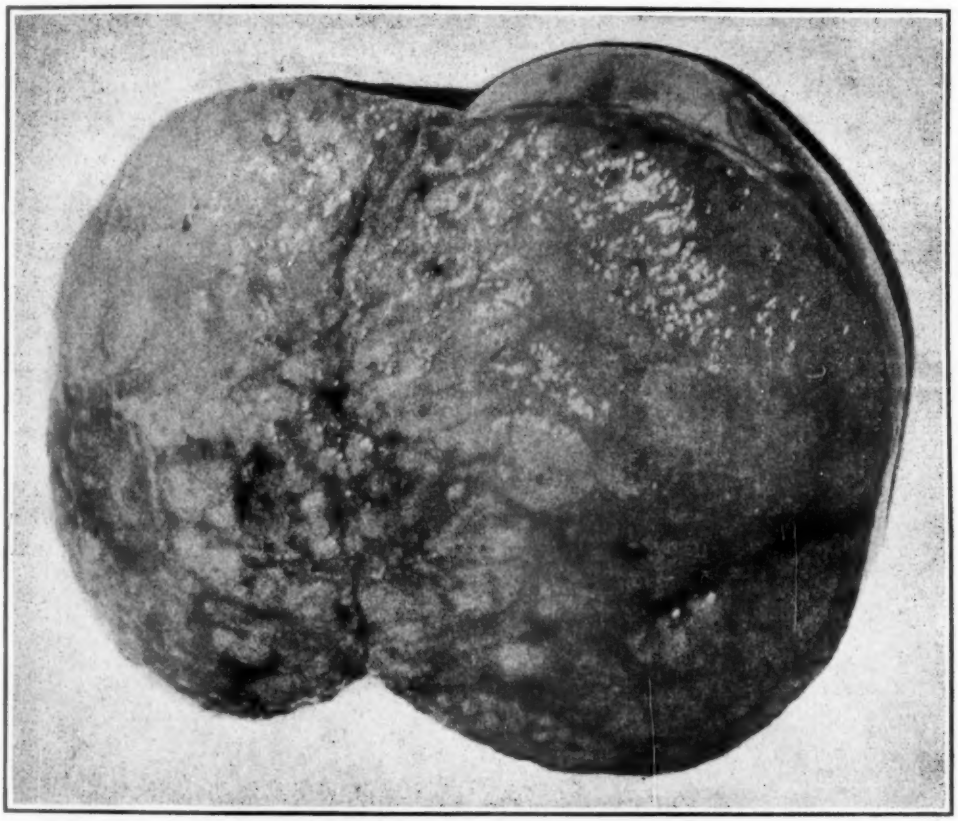

FIGURE 2. *Photograph of the Tumor after Removal.*

The wisdom of demonstrating an adequate adrenal gland on the side opposite the tumor is apparent from this case. It was so obvious, however, that the patient's well-being and life were jeopardized by the tumor that its immediate removal seemed justified, and the ultimate outcome would have been the same had surgery been withheld.

State of the Adrenal Gland Opposite to That Containing Tumor

Although it had previously been noted that in tumor of the adrenal cortex the contralateral gland exhibited varying degrees of atrophy, Cecil,[25] in 1933, was the first to emphasize this fact when he reviewed the literature and found that in 30 per cent of cases the adrenal gland on the side opposite the tumor was either absent or atrophic to an extent insufficient to support life. Cecil considered the process in cases of reported absence of the gland to be one of advanced atrophy rather than true aplasia.

In 1941 Weinberg,[26] in a review of 34 cases of neoplasm of the adrenal cortex occurring in the preceding fourteen years in which the clinical observations on the state of both adrenal glands had been confirmed at autopsy, found that atrophy was encountered in 21 cases, or 62 per cent, and that the gland was completely absent in 2 cases. In 10 cases the gland was reported as "grossly normal." He also described a case in which bilateral adrenal atrophy had been caused by a tumor of an accessory adrenal gland.

The cause of this glandular atrophy on the supposedly normal side is excess production of the metabolic hormones by the tumor, with consequent suppression of function of the normal tissue. From the teleologic standpoint, the tumor relieves the normal gland of the necessity of functioning. Examples of this process in other endocrine glands are found in the involution of the insulin-forming beta cells of the pancreas that accompanies tumors of the islands of Langerhans, and the atrophy of the normal parathyroid glands that takes place in the presence of a parathyroid tumor. Furthermore, excess administration of estrogenic substances has been noted to cause involution of the ovaries, and similar changes in the testicles have been induced by excess androgenic hormone injection. Selye[27] has proposed the term "compensatory atrophy" for this phenomenon.

From the experimental point of view, Ingle and Kendall[28] started with the observation that transplants of the adrenal glands do not regenerate in the presence of one intact gland and demonstrated that the administration of large amounts of cortin to normal rats produced atrophy of the adrenal cortex. They found this effect to be mediated through the adrenotropic principle of the anterior portion of the pituitary gland.

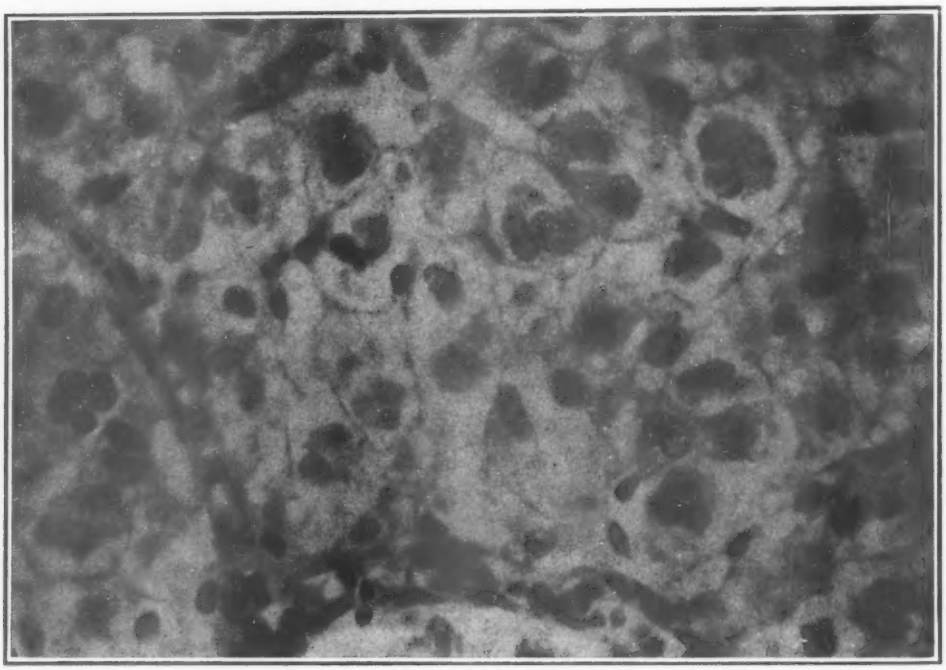

Figure 3. *Photomicrograph of a Section of the Tumor.*

In 1926 Feinblatt[29] reported the case of a thirty-two-year-old woman with virilism dying of exhaustion, who at autopsy showed a carcinoma of the right adrenal gland and a complete absence of the one on the left. In 1927 Gordon and Browder[30] described a case of a left suprarenal carcinoma causing puberty praecox in a three-year-old boy who died of pulmonary metastases, and at autopsy no suprarenal gland was found on the right. Lukens et al.,[31] in 1937, reported the case of a twenty-nine-

year-old woman with Cushing's syndrome who was operated on with removal of an encapsulated tumor from the right adrenal gland and died on the eighth postoperative day of shock. Autopsy revealed complete absence of the left adrenal gland and the residual adrenal tissue on the right side to be about half the normal size. Lukens stated that the autopsy files of the University of Pennsylvania Hospital from 1894 to the date of his report contained records of 3 additional cases of absence of the gland; none, however, had been associated with contralateral tumor. Absence of the left adrenal gland was found on surgical exploration by Goldheizer[32] in the case of an eighteen-year-old girl with hirsutism; the right adrenal gland in this case was enlarged, but no extirpation of tissue was done in view of the missing left gland.

Cahill,[2] using perirenal insufflation in investigating several hundred cases of suspected adrenal disease, found that in 9 per cent only one adrenal gland could be demonstrated by this method.

Treatment

The treatment of these tumors is primarily by surgical removal. The operation is doomed to failure, however, unless a carefully planned program to counteract postoperative acute adrenal insufficiency due to reduced function of the opposite gland is carried out. According to Cahill the most important factor in the surgical management of these cases is the anticipation, prevention or control of such failure.

At the time of the operation it is essential to determine both the presence of the supposedly normal gland and its capacity to support life. In some cases in which the opposite gland was described as half the normal size, the patients have recovered.[33]

From the technical standpoint, two surgical approaches are frequently used — namely, the lumbar extraperitoneal route and the abdominal transperitoneal route. Transthoracic access to the adrenal glands has been described but has found little popularity in the literature. Walters[33] recommends exposure of both glands and uses the usual loin-kidney incision. Young[34] explores both glands simultaneously through the lumbar regions, using a specially devised spreader type of retractor. Cahill[5] recommends the anterior, abdominal, transperitoneal approach through an oblique subcostal incision as giving the best exposure and permitting exploration of the opposite gland through the same incision.

All who have had experience with the surgical removal of tumors of the adrenal cortex emphasize that immediate aggressive postoperative steps must be taken to combat acute adrenal insufficiency. The majority of deaths occur in from twenty-four to forty-eight hours after operation of collapse, which does not respond to the usual antishock therapy of fluids, blood transfusion and stimulants. If adequate amounts of adrenocortical extract are given, however, it may be expected that the remaining adrenal tissue will regain its capacity to produce a sufficient amount of the hormones essential to life. Walters, who has successfully operated on 10 patients, attributes his success to the availability of potent adrenocortical preparations to tide the patient over the critical period immediately after operation.

In a case of Cushing's syndrome due to an adenoma in which the patient was successfully operated on, Wilhelm and Gross[16] used the blood-pressure readings as a guide for the dosage of adrenocortical extract. They point out that there is a danger of overdosage as shown by the development of oliguria and anasarca from the seventh to the twelfth postoperative day. Grollman[35] suggested a dosage of 200 rat units of adrenocortical extract a day as appropriate for the immediate postoperative period.

Prognosis

It should be recalled that postoperative fatalities are much more frequent in the cases with metabolic changes than in those in which sexual changes predominate.

In 1933 Cecil[25] stated that in 39 per cent of the operated cases the patients died of shock caused by adrenal deficiency. In 1941 Weinberg[26] wrote that the outcome is usually fatal shortly after surgery. In 1943 Thompson and Eisenhardt[12] found that in 22 cases of adrenal tumor with Cushing's syndrome, 18 patients who were operated on with removal of the tumor died in the immediate postoperative period of shock resembling adrenal insufficiency. In a few cases death occurred in spite of "fairly adequate" measures to combat the deficiency.

Summary

The subject of hormone-producing tumors of the adrenal glands is reviewed, with reference to classification, relation to Cushing's syndrome, diagnosis, treatment and prognosis.

A case of Cushing's syndrome due to an adrenal tumor is reported in which the patient died of acute adrenal insufficiency thirty-six hours after operative removal of the tumor and in which, at autopsy, complete absence of the opposite adrenal gland was found. This is the fourth such case in the literature.

From a review of the available literature it is concluded that an increasing number of successful operative removals are being done owing to better postoperative therapy. The prognosis, however, is still exceedingly grave in the cases associated with Cushing's syndrome, because of the atrophy and insufficiency of the supposedly normal gland.

References

1. Grollman, A. K. *The Adrenals.* 410 pp. Baltimore: Williams and Wilkins Company, 1936.
2. Cahill, G. F. Tumors of adrenal and use of air insufflation in their diagnosis. *Radiology* 37:533-544, 1941.

3. Cahill, G. F., Melicow, M. M., and Darby, H. H. Adrenal cortical tumors: types of nonhormonal and hormonal tumors. *Surg., Gynec. & Obst.* **74**:281-305, 1942.
4. Cahill, G. F. Hormonal tumors of adrenal gland. *Pennsylvania M. J.* **47**:655-667, 1944.
5. *Idem.* Hormonal tumors of adrenal. *Surgery* **16**:233-265, 1944.
6. Collett, A. Genito-suprarenal syndrome (suprarenal virilism) in girl one and a half years old, with successful operation. *Am. J. Dis. Child.* **27**:204-218, 1924.
7. Simpson, S. L., and Joll, C. A. Feminization in male adult with carcinoma of adrenal cortex. *Endocrinology* **22**:595-604, 1938.
8. Cushing, H. Basophil adenomas of pituitary body and their clinical manifestations (pituitary basophilism). *Bull. Johns Hopkins Hosp.* **50**:137-195, 1932.
9. Susman, W. Adenomata of pituitary, with special reference to pituitary basophilism of Cushing. *Brit. J. Surg.* **22**:539-544, 1935.
10. Dorfman, R. I., Wilson, H. M., and Peters, J. P. Differential diagnosis of basophilism and allied conditions. *Endocrinology* **27**: 1-15, 1940.
11. Farber, J. E., Gasteria, F. J., and Postoloff, A. V. Cushing's syndrome in children: review of literature and report of case. *Am. J. Dis. Child.* **65**:593-603, 1943.
12. Thompson, K. W., and Eisenhardt, L. Further consideration of Cushing syndrome. *J. Clin. Endocrinol.* **3**:445-452, 1943.
13. Anderson, E., and Haymaker, W. Cushing's syndrome. *J. Nerv. & Ment. Dis.* **99**:511-520, 1944.
14. Lukens, F. D. W. Diagnosis and treatment of disorders of adrenal glands. *M. Clin. North America* **26**:1803-1815, 1942.
15. Frank, R. T. Estrogenic reaction in adrenal cortical carcinoma. *J. Mt. Sinai Hosp.* **8**:514-519, 1942.
16. Wilhelm, S. F., and Gross, S. W. Surgical removal of adrenal adenoma with relief of Cushing's syndrome. *Am. J. M. Sc.* **207**:196-204, 1944.
17. Reilly, W. A. Adrenal cortical tumor causing sexual precocity, including successful treatment of coma shock and hemorrhage preceding operation. *Clinics* **1**:669-676, 1942.
18. Oppenheimer, B. S., and Silver, S. Variability in pathological findings in Cushing's syndrome: report of six cases. *Tr. A. Am. Physicians* **52**:146-163, 1937.
19. Gross, R. E. Neoplasms producing endocrine disturbances in childhood. *Am. J. Dis. Child.* **59**:579-628, 1940.
20. Talbot, N. B., Butler, A. M., and Berman, R. A. Adrenal cortical hyperplasia with virilism: diagnosis, course and treatment. *J. Clin. Investigation* **21**:559-570, 1942.
21. Fish, G. W. Discussion of Roome.[23]
22. Cope, O., and Schatzki, R. Tumors of adrenal glands. I. Modified air injection roentgen technic for demonstrating cortical and medullary tumors. *Arch. Int. Med.* **64**:12222-1238, 1939.
23. Roome, N. W. Visualization of adrenal glands by air injection. *J. A. M. A.* **112**:196-198, 1939.
24. Hyman, A., and Wilhelm, S. F. Differential diagnosis of renal and suprarenal tumors. *J. Urol.* **40**:737-751, 1938.
25. Cecil, H. L. Hypertension, obesity, virilism and pseudohermaphroditism as caused by suprarenal tumors. *J. A. M. A.* **100**:463-466, 1933.
26. Weinberg, T. Contralateral adrenal atrophy associated with cortical adrenal neoplasms. *New York State J. Med.* **41**:884-886, 1941.
27. Selye, H. Compensatory atrophy of adrenals. *J. A. M. A.* **115**: 2246-2252, 1940.
28. Ingle, D. J., and Kendall, E. C. Atrophy of adrenal cortex of rat produced by administration of large amounts of cortin. *Science* **86**: 245, 1937.
29. Feinblatt, H. M. Carcinoma of cortex of suprarenal gland with virilism: report of case with necropsy. *Arch. Int. Med.* **38**:466-473, 1926.
30. Gordon, M. B., and Browder, E. J. Suprarenal carcinoma with pubertas praecox in boy three years of age. *Endocrinology* **11**: 265-278, 1927.
31. Lukens, F. D. W., Flippen, H. F., and Thigpen, F. M. Adrenal cortical adenoma with absence of opposite adrenal report of case with operation and autopsy. *Am. J. M. Sc.* **193**:812-820, 1937.
32. Goldheizer, M. A. *The Adrenal Glands in Health and Disease.* 739 pp. Philadelphia: T. A. Davis Company, 1945. P. 525.
33. Walters, W. Surgical lesions of adrenal glands. *South. M. J.* **34**: 1241-1247, 1941.
34. Young, H. H. *Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases.* 649 pp. Baltimore: Williams and Wilkins Company, 1937.
35. Grollman, A. Personal communication.

ACUTE APPENDICITIS OCCURRING DURING THE COURSE OF OTHER DISEASES*

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THE diagnosis of acute appendicitis is usually considered whenever a patient develops symptoms or signs suggesting an acute intra-abdominal inflammatory lesion. There are many contributions dealing with the differential diagnosis of abdominal symptomatology, in which many diseases that mimic appendicitis are enumerated and classified. The inference usually drawn is that laparotomy on the basis of an erroneous diagnosis of acute appendicitis is warranted if some morbid process is encountered to account for the clinical picture, such as a twisted ovarian cyst, inflamed Meckel's diverticulum, regional ileitis, neoplasm, volvulus or intussusception. Emphasis is usually placed, however, on the dangers of operating on a patient whose abdominal complaints are based on some other underlying systemic or regional disorder. Prominent among the more frequent of these diseases are pneumonia, tonsillitis, upper respiratory infections, pyelitis, cardiac failure, mesenteric thrombosis, diabetic ketosis and syphilis of the central nervous system. It is beyond the scope of this communication to undertake a discussion of these diseases and the features in the differential diagnosis that distinguish them from appendicitis. The problems of diagnosis and operative indications are particularly complicated in patients already hospitalized, or under treatment for some nonrelated disorder, who, under observation, develop acute abdominal complaints referable to the lower abdomen. Although under ordinary circumstances such symptoms are sufficiently specific to warrant a diagnosis of appendicitis, under these special conditions there is a tendency to dismiss the possibility of an independent lesion, and to attempt to correlate the new symptomatology with the pre-existent disorder. The delay in therapy thus engendered may be prejudicial to the interests of the patient, whose best chance for recovery may depend on removal of the acutely inflamed appendix.

It is the purpose of this paper to emphasize the necessity for laparotomy in the presence of persisting symptoms and signs ordinarily associated with acute appendicitis, despite the pre-existence or coexistence of other diseases that include abdominal complaints among their possible manifestations. The following cases are illustrative.

CASE 1. J. T. (M.S.H. 503817), an 8-year-old girl, previously in good health, was admitted to the hospital on April 6, 1943, suffering from an acute respiratory infection of 24 and abdominal pain of 6 hours' duration. On the previous day, she had begun to cough, and a sore throat and coryza had been noted. Six hours before admission she had begun to experience abdominal pain localized to the region of the umbilicus and had vomited three times. On examination, the temperature was 98.8°F., the pulse 78, and the respirations 24. A purulent pharyngitis was present.

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together with greatly enlarged, reddened tonsils. There was a generalized lymphadenopathy, and the spleen was palpated one fingerbreadth below the left costal margin. The abdomen was soft, with persistent tenderness in the right lower quadrant. Rectal examination disclosed no tenderness. Examination of the blood revealed a white-cell count of 18,100, with 73 per cent neutrophils and 22 per cent lymphocytes. An appendectomy performed shortly after admission disclosed an acute phlegmonous appendicitis. The convalescence was uneventful. A throat culture revealed beta-hemolytic streptococcus and alpha-hemolytic streptococci. Blood for heterophil agglutination was positive in a dilution of 1:16.

Case 2. A. C. (M.S.H. 486225), a 14-year-old boy, was admitted to the hospital on February 27, 1942, with a history of abdominal pain, which had shifted to the right lower quadrant, and vomiting of 2 days' duration. The onset of pain was associated with a sore throat and a temperature of 101°F. On examination, the temperature was 101°F., the pulse 80, and the respirations 20. The patient appeared acutely ill, and complained of severe pain in the lower abdomen. There was a marked postnasal discharge, and white follicles were present on the right tonsil. The peripheral lymph nodes were slightly enlarged. Lower abdominal tenderness was present, chiefly in the right lower quadrant, with some rigidity to the right of the umbilicus. Rectal examination revealed tenderness on the right side. Urinalysis showed a slight trace of albumin. Shortly after admission, an appendectomy was performed, the appendix revealing acute inflammation. The nasopharyngitis subsided, and the patient was discharged on the 8th postoperative day.

Case 3. O. G. (M.S.H. 454412), a 32-year-old painter, was admitted to the hospital on March 29, 1940, with complaints of a severe sore throat, general malaise and fever of 3 days' duration. During 12 hours prior to admission he had experienced pain in the right lower quadrant, with radiation to the epigastrium, followed by vomiting. The pain in the lower abdomen became progressively severer. On examination, the temperature was 100°F., the pulse 92, and the respirations 26. The patient appeared acutely ill. Marked follicular tonsillitis was present. There were both tenderness and spasm in the right lower quadrant. Appendectomy was performed promptly, and an acute gangrenous appendicitis was encountered. Postoperatively the temperature rose to 104°F., associated with an increase in the follicular tonsillitis. Sulfanilamide was given, and the temperature subsided to normal on the 4th day, with corresponding clinical improvement. The wound healed by primary union, and the patient was discharged on the 8th postoperative day.

Case 4. H. B. (M.S.H. 488688), a stocky 50-year-old man, was admitted to the hospital on April 21, 1942, complaining of lower abdominal pain of 48 hours' duration. The diagnosis of diabetes mellitus had been established 15 years previously, and the disease had been controlled during this period by dietary regulation without insulin. On examination, the temperature was 100.2°F., the pulse 90, and the respirations 26. Moderately advanced neuroretinopathy was present. There was localized tenderness, without spasticity, in the right lateral portion of the abdomen near the level of the umbilicus; no tenderness could be elicited on rectal examination. Urinalysis revealed a ++++ test for sugar but no acetone. During a 24-hour period, the diabetes was brought under control with insulin; there was no increase in symptomatology, and no further temperature elevation. Lower abdominal pain and tenderness persisted, and operation disclosed the appendix as the seat of an acute phlegmonous inflammation. The postoperative course was uneventful, the wound healing by primary union, and the patient was discharged on the 12th day, when he was receiving 20 units of protamine insulin daily and was sugar free on a daily diet of 150 gm. of carbohydrate, 80 gm. of protein and 80 gm. of fat.

Case 5. L. S. (M.S.H. 497398), a moderately obese, 45-year-old man, entered the hospital in November, 1942, with an acute myocardial infarction, pericarditis and cardiac decompensation. A subtotal gastrectomy for duodenal ulcer had been performed in July, 1938, after 9 years of unsuccessful medical treatment. On admission, the temperature was 102°F., the pulse 100, and the respirations 30. A pericardial friction rub was present, and the heart sounds were of only fair quality; coarse rales were heard at both lung bases. The electrocardiographic changes were those of an acute infarction of the posterior wall. On the 3rd hospital day the patient developed a left hemiparesis, which was attributed to a cerebral embolus from a detached mural thrombus. The temperature gradually subsided, the sedimentation time rose to normal, the friction rub became intermittent, and the signs of both the hemiparesis and the congestive failure began to clear. Thirty-seven days after admission, lower abdominal cramps, followed by nausea and vomiting, developed. There was tenderness without spasm in the right lower quadrant, and some tenderness to the right on rectal examination. The temperature remained normal. Examination of the blood showed a white-cell count of 15,300, with 78 per cent neutrophils — 2 weeks previously the white-cell count had been 11,200, with 66 per cent neutrophils. Examination of the stool for occult blood was negative.

Because of the bizarre clinical course, with recurrent pericarditis, pneumonia, hemiparesis and microscopic hematuria, the possibility of a vascular basis for the abdominal symptomatology was considered. Among the diagnoses entertained were mesenteric thrombosis and periarteritis nodosa. The patient was observed for about 8 hours, during which the symptoms and signs persisted without much change. After a surgical consultation laparotomy was performed, disclosing acute phlegmonous appendicitis. The postoperative course was uneventful.

Case 6. F. P. (M.S.H. 503343), a 32-year-old man, was admitted to the hospital on March 26, 1943. He had been awakened 8 hours previously by pain in the right lower quadrant that was nonradiating and was associated with nausea, without vomiting. Three years previously he had contracted syphilis and gonorrhea, both of which had been treated intensively; antisyphilitic therapy was still being administered. On examination, the temperature was 100°F., the pulse 108, and the respirations 32. There was tenderness in the right lower quadrant, with slight spasm. Rectal examination disclosed tenderness to the right. Despite the clear-cut evidence of acute appendicitis, there was a tendency on the part of some observers to interpret the clinical picture in terms of syphilitic changes. Appendectomy was promptly performed, however, and disclosed an acute phlegmonous appendicitis.

Case 7. R. L. (M.S.H. 452212), a 13-year-old girl, with an indefinite 4-year history of "kidney trouble," was admitted to the hospital on February 7, 1940. On the morning of admission she complained of abdominal distress, followed by severe epigastric cramps, vomiting and radiation of the pain to the right lower quadrant. A similar episode had occurred 1 year previously. On examination the patient did not appear acutely ill. The temperature was 102°F., the pulse 140, and the respirations 28. The abdomen was soft, with slight generalized tenderness referred to the right lower quadrant and maximum direct tenderness just below McBurney's point. There was slight rectal tenderness on the right. The white-cell count was 12,800, with 92 per cent neutrophils. Urinalysis showed a ++++ test for albumin, with many coarse cellular casts and rare red cells per high-power field. The blood urea nitrogen was 9 mg. per 100 cc.; the blood Wassermann reaction was negative. In spite of the chronic glomerulonephritis and the atypical clinical picture, appendectomy was performed on the 2nd hospital day because of the persistence of spontaneous pain and tenderness. Acute appendicitis and lymphoid hyperplasia were found. The postoperative course was smooth, but characterized by persistent albuminuria and a blood pressure ranging about 150/80.

Case 8.* H. C. (M.S.H. 450278), an 18-year-old Negro, was admitted to the hospital on December 23, 1939. For 2 years there had been an intermittent purulent discharge from the right ear. Stiffness of the right side of the face and drooping of the right side of the mouth had been increasingly more troublesome for the preceding 4 days. Several months previously the patient had worked for a short time at the Bronx Zoo. The temperature, pulse and respirations were normal.

Physical examination disclosed a well developed and well nourished man lying quietly in bed with eyes closed, head drawn back, legs extended and arms flexed. There was a coarse horizontal nystagmus on left lateral gaze; the eye

*This case was reported, with special reference to the otologic features, by Rosen.[1]

grounds were not remarkable. A posterior marginal perforation of the right ear drum was present, with a small amount of thin, pulsating, nonfoul discharge; there was no tenderness over the mastoid process. The left ear drum was normal. Slight trismus was noted. Boardlike rigidity of the abdominal musculature was present, without tenderness. There was considerable increase in tone in the arms, and passive movement of the legs was difficult because of rigidity. The neck could not be flexed, but could be moved from side to side. The tendon reflexes in the arms were depressed, and those in the legs were decreased and jerky. No pathologic reflexes could be elicited. The patient was rational and talked slowly and carefully.

Shortly after admission the patient experienced a generalized, true tetanic convulsion, characterized by marked opisthotonos, without clouding of consciousness. Several such episodes occurred within a short period, each precipitated by noise or trauma, such as movement. A lumbar tap revealed clear spinal fluid under normal pressure, with normal dynamics; there were no significant cellular or chemical changes. The convulsive state soon became quite difficult to control, and almost constant opisthotonos was present. Extremely deep anesthesia was needed to obtain relaxation, and within a 5-hour period the patient received 70 mg. of Avertin per kilogram of body weight by rectum and 0.5 gm. of sodium amytal, and 100 mg. of Avertin per kilogram of body weight intravenously as well as deep ether anesthesia. Despite all sedation the rigidity persisted, and it was necessary to repeat the ether frequently. On the night after the practically permanent convulsive state, marked stridor developed, and artificial respiration was required several times. Because of extreme swelling of the tongue and episodes of laryngeal spasm, a tracheotomy was performed.

Large doses of tetanus antitoxin were administered intravenously — 100,000 units a day for 2 days, followed by 50,000 units every other day, with a progressive reduction to 5000 units every 3 days. On the day after the onset of the convulsions the temperature rose to 104°F., the pulse to 140, and the respirations to 50 to 60, and the patient became incontinent. A bilateral bronchopneumonia, involving large portions of both lower lobes, was treated by 0.6 per cent sulfapyridine intravenously. The white-cell count rose from normal to 15,000, but a blood culture was negative. At the end of 5 days the patient's condition was still poor, with a temperature of 105°F. and gasping respirations. Although the tetanic state was gradually being controlled, the treatment of the pneumonia was the chief problem, and the patient required an oxygen tent and constant special nursing care. At that time smears taken from the right ear were reported as showing a variety of organisms, including proteus and tetanus bacilli and the enterococcus. The pathogenicity of the tetanus bacilli was established by demonstration of their toxin-producing properties on bacteriologic investigation. There was a gradual recession of the rigidity, and the pneumonia slowly cleared. The temperature returned to normal, the tachycardia persisted, and there were occasional mild serum reactions.

A month after admission, while approaching convalescence, the patient developed abdominal cramps, without vomiting. The abdominal wall presented the extreme rigidity characteristic of tetanus, and there was localized tenderness over McBurney's point. In addition, there was evidence of mild serum sickness, with generalized lymphadenopathy and eosinophilia. Over a period of 12 hours' observation, the symptoms and signs persisted unchanged. The temperature remained normal. Examination of the blood showed a white-cell count of 14,900, with 68 per cent segmented, and 14 per cent nonsegmented neutrophils, 15 per cent eosinophils and 3 per cent monocytes; 8 days previously the count had been 11,300, with 44 per cent segmented and 8 per cent nonsegmented neutrophils, 31 per cent lymphocytes, 12 per cent monocytes and 5 per cent eosinophils. Despite the obvious reasons for possible temporizing in this case, operation appeared imperative once the diagnosis of acute appendicitis had been made. The patient was given 120 mg. of procaine as a spinal anesthetic, with no demonstrable relaxation of the abdominal musculature. The pathological report was: "acute phlegmonous appendicitis."

Following recovery the patient underwent a modified right radical mastoidectomy, in an attempt to eliminate the primary focus of the tetanus. He was discharged from the hospital on March 4, and the tracheotomy was allowed to close. Follow-up observation for 2 years showed him to be in good general health.

Case 9. F. L. (M.S.H. 501896), a 22-year-old man in good health, was admitted to the hospital on February 19, 1943, for the repair of a small, asymptomatic, right, indirect, inguinal hernia that had been detected in the course of a physical examination for induction into the Navy. There were no other physical defects. Urinalysis was negative; the white-cell count was 8300. On February 20, a right herniorrhaphy was performed under local (novocain) anesthesia. During the 1st week the postoperative course was uneventful, and the temperature at no time rose above 99°F. The patient was awakened at 4 o'clock on the morning of the 8th postoperative day with pain below the umbilicus, followed by nausea and unsuccessful attempts to vomit. The temperature was 97°F., and the pulse rate 60. The pain subsided in a short while, after the passage of flatus. Abdominal examination disclosed slight tenderness in the right lower quadrant, without spasm. There was no evidence of a wound infection. Under observation, slight pain recurred in the right lower quadrant, and the tenderness became more marked. The temperature rose to 99°F., the white-cell count to 12,800, with 90 per cent segmented and 3 per cent nonsegmented neutrophils. An appendectomy was performed 15 hours after the onset of symptoms. Pathological examination disclosed an acute phlegmonous appendicitis. Convalescence thereafter was without incident.

Case 10. E. Y. (M.S.H. 502446), a 10-year-old girl, was admitted to the hospital in March, 1943. Three years previously, following aspiration of an Indian nut, she had been treated at another hospital for "pneumonia," and a thoracotomy had been performed for empyema. The evidence of pulmonary suppuration had persisted. Shortly after admission a lobectomy of the left upper lobe, performed for numerous nonputrid pulmonary abscesses, was followed in 10 days by a drainage operation for empyema. On the 14th postoperative day the patient became nauseated and vomited several times; but there was no abdominal pain or tenderness. On the following day she was still nauseated, but did not vomit. She complained of periumbilical pain, and there was direct tenderness in the right lower quadrant. The pulmonary status contraindicated any surgery unless it was imperative.

An appendectomy revealed acute appendicitis. The patient withstood the operation well. Two weeks later a left hemiparesis developed, and death occurred on the day after operation for a large metastatic brain abscess secondary to intrathoracic suppuration.

These cases are not unique. They were selected, not from a review of the hospital records but from the large number of cases of acute appendicitis seen on an active surgical service over a three-year period. In common, they all represented appendicitis occurring in the course of other diseases.

The first 3 cases illustrate one of the most frequent problems concerned with abdominal symptomatology. Leaving aside the moot question of the relation between tonsillar (and upper respiratory) infection and acute appendicitis, the widespread distribution of upper respiratory infections during the winter months makes its coincidence with acute appendicitis inevitable in some patients. Although an unnecessary laparotomy performed on a patient with tonsillitis or an upper respiratory infection may contribute to the development of a more serious pulmonary complication, the consequences of neglecting an acutely inflamed appendix may be even more profound. Fever may be due to obvious nasopharyngitis or to a suspected appendicitis. The presence of a leukocytosis, as demonstrated either by the total white-cell count or by the differ-

ential count, is of no differential aid. Attention is called to the study of Medlar,[2] who in 1929 analyzed the variations in the white-cell counts of normal persons. In the series of 506 children with acute appendicitis reported by Scott and Ware,[3] the white-cell count was below 10,000 in 17 children who presented perforation with peritonitis or abscess. In 1 case (M.S.H. 497693), the white-cell count fell from 11,000 to 7500 in a patient with pain in the right lower quadrant and microscopic hematuria who was suspected of harboring a ureteral calculus; the disease was revealed at operation to be acute phlegmonous appendicitis. The current attitude of most surgeons on the subject of the white-cell count in the diagnosis of acute appendicitis may be summed up in Johnson's[4] plea not to trust blindly to a low white-cell count as conclusive evidence against appendicitis, or to a high one as overwhelming evidence in favor of operation, and by a similar statement in a review of cases of appendicitis in pregnancy by Twyman, Mussey and Stalker.[5] In the presence of an acute upper respiratory infection the diagnosis of appendicitis must rest on clinical grounds.

The evaluation of abdominal pain in a person suffering from diabetes, cardiac disease, syphilis or nephritis involves many considerations. The point to be made is that these patients possess the same potentialities for developing acute appendicitis as other persons; episodes of abdominal symptoms and signs ordinarily suggestive of acute appendicitis should continue to be so regarded. Indeed, it can be contended with considerable justification that a patient suffering from a serious systemic disease has a far greater chance for survival if operated on in the uncomplicated than in the later stages of acute appendicitis. A similar situation exists in abdominal pain in the course of the contagious diseases of childhood. In the series reported by Goodman and Silverman,[6] in more than half the cases of acute appendicitis, the appendix was found to have perforated at the time of operation. Delayed operation was at least in part attributable to an attempt to interpret the abdominal pain as a possible manifestation of the infectious disease. The difficulty of establishing an early diagnosis in young children is further attested by Scott and Ware,[3] who point out that in children under six years of age perforation was encountered more than twice as often as simple acute appendicitis without rupture.

In the case of tetanus (Case 8) presented above, many unusual medical and otologic features were evident and the abdominal rigidity rendered the diagnosis of an acute intraperitoneal inflammatory process difficult. In the patient convalescing from a right-sided hernioplasty performed a week previously (Case 9), careful consideration had to be paid both to the site and to the circumstances of the first operation. Case 10 illustrates the occurrence of acute appendicitis in the course of unrelated pulmonary suppuration.

Acute appendicitis has been recorded in the course of acute anterior poliomyelitis,[7] Addison's disease[8] and pneumonia with malaria.[9] Although regarded as unusual among the newborn and the aged, acute appendicitis has been reported in a sixteen-day-old infant.[10] And with the increase in the life expectancy of the population, more and more cases in the older age groups are encountered.

It is an established surgical principle that the possible complications of acute appendicitis can best be avoided by prompt appendectomy during the early period of the inflammatory process. The favorable influence of the sulfonamides and newer chemotherapeutic agents on the prognosis in the severer forms of acute appendicitis cannot be advanced as a valid argument for temporizing. A short interval from the onset of the symptoms and signs of acute appendicitis is still the optimum time of operation, and this principle cannot be compromised because acute appendicitis may occur during the course of other diseases.

Summary

Ten representative cases of acute appendicitis occurring in the course of other diseases are presented.

The tendency to interpret such cases as possible manifestations of the underlying disease rather than as an independent intraperitoneal lesion is pointed out. The consequences of a temporizing attitude in terms of the increased morbidity of appendiceal peritonitis is discussed.

Acute appendicitis must be diagnosed on the basis of clinical evidence (symptoms and signs) regardless of any coexisting disease.

References

1. Rosen, S. Otogenous tetanus. *J. Mt. Sinai Hosp.* 8:96, 1941.
2. Medlar, E. M. Extent of variations in the leukocytes of normal individuals. *Am. J. M. Sc.* 177:72-87, 1929.
3. Scott, H. W., Jr., and Ware, P. F. Acute appendicitis in childhood. *Arch. Surg.* 50:258-268, 1945.
4. Johnson, A. S. Reliability of leukocyte count in diagnosis of appendicitis. *New Eng. J. Med.* 223:373-376, 1940.
5. Twyman, R. A., Mussey, R. D., and Stalker, L. K. Appendicitis in pregnancy: review of 75 cases. *Proc. Staff Meet., Mayo Clin.* 15: 484-487, 1940.
6. Goodman, M., and Silverman, I. Acute appendicitis in patients with common contagious diseases. *New Eng. J. Med.* 228:533-542, 1943.
7. Metheney, D., and Olson, H. H. Appendectomy on poliomyelitis patient in Drinker respirator. *West. J. Surg.* 53:88, 1945.
8. Laipply, T. C. Addison's disease due to cytotoxic contraction of adrenal cortex with sudden death four days after appendectomy. *Ohio State M. J.* 39:652, 1943.
9. Flowers, S. H. Pneumonia, malaria, appendicitis in one case. *Kentucky M. J.* 42:143, 1944.
10. Wilson, W. E. Appendicitis in newborn: report on case 16 days old. *Proc. Roy. Soc. Med.* 38:186, 1945.

ASIATIC SCHISTOSOMIASIS*

Report of an Early Case

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THE following case of acute Asiatic schistosomiasis was unique in that an opportunity was afforded to follow the clinical course with repeated sigmoidoscopies and serial roentgenograms from the onset of symptoms to the termination of a course of treatment — a period of sixty days. More informative accounts of the disease are given by Billings, Winkenwerder and Hunninen,[1] Thomas and Gage,[2] Faust et al.[3] and others.[4]

A 19-year-old soldier of Italian descent was admitted to the 117th Station Hospital on Leyte, Philippine Islands, on December 19, 1945, with a chief complaint of "hives." He stated that about 30 days previously he had been exposed to the infected waters of a tributary of the Palo River and immersed from feet to waist for about 3 hours. He had noticed no swimmers' itch during the next 48 hours and had felt entirely well until the onset of urticaria 2 days before admission. The past history was essentially unremarkable except for an attack of urticaria 5 years previously when the patient had been living in New York City. The family history was negative for allergic diseases.

Physical examination disclosed giant urticarial lesions of the face, torso and extremities. The spleen and liver were just palpable on deep inspiration, and both organs were firm and not tender. The remainder of the physical examination was negative.

During the 1st week in the hospital urticaria was intermittent and associated with angioneurotic edema of the right cheek and infraorbital tissues and the dorsum of the right foot. These lesions cleared after 8 days and did not recur. The white-cell count, which on December 21 was 9850, with 6 per cent eosinophils, on December 26 was 6250, with 10 per cent eosinophils. Sigmoidoscopy on the day after admission showed no nodular lesions of the rectosigmoid region characteristic of schistosomiasis.

On December 24 the temperature, which had been normal, rose to 102°F., with a proportionate elevation of the pulse. Other complaints were anorexia, nausea and moderately severe colicky epigastric pain, which remained troublesome for the next 3 weeks. The temperature and pulse remained intermittently elevated for 24 days, the temperature varying between normal and 103°F., and the pulse between 70 and 120.

On December 25 a dry cough developed and was associated with sibilant rhonchi and a few fine crepitant rales in both lungs. An x-ray film of the chest taken on December 27 showed multiple patches of increased density scattered throughout both lung fields, with increased prominence of the bronchovascular markings.‡ Concentrated stool specimens on December 31 and January 2, 3 and 4 were guaiac negative. On January 5 a repeated chest plate showed a definite change in the distribution of the areas of increased density.

On January 3 sigmoidoscopy for the first time revealed disease of the rectosigmoid. Several distinctly erythematous areas and erythematous nodular lesions measuring 1 or 2 mm. in diameter were visualized. The nodules did not have the yellow color ascribed to typical lesions of schistosomiasis and did not offer the characteristic resistance with clicking sensation to the lip of the sigmoidoscope. A smear of mucus taken from the surface of one of the nodules was negative for ova. Concentrated stool specimens were negative for ova on January 5 and 7. Cysts of *Entamoeba histolytica*, however, were found on the latter date and again on January 8. Sigmoidoscopy was repeated on January 9, and ten to twelve nodular lesions, similar to those previously observed, were visualized in the same region of the rectosigmoid. The nodules, which were more prominent and offered resistance to the lip of the sigmoidoscope in the typical fashion, were still red. A few pinpoint erythematous lesions were considered typical of amebiasis. A biopsy specimen of one of the nodules was negative on direct examination, probably because a deep enough bite had not been taken.

In the meantime, the patient was running a fever, complaining of severer pains in the upper abdomen and right upper quadrant. There was some increased tenderness of the liver edge to palpation, and the area of liver dullness had become tenderer to light percussion. On January 7 the white-cell count was 20,150, with 64 per cent neutrophils, 14 per cent eosinophils and 22 per cent lymphocytes. Although a diagnosis of schistosomiasis japonica seemed likely, it was considered advisable, in the lack of definite proof, to try a 6-day course of emetine hydrochloride to evaluate the effect of amebic infection on the liver symptoms and the fever. There was no response of temperature or symptoms to emetine. A chest plate on January 11 showed some increase in the patchy nodular lesions in both lung fields without significant change in the bronchovascular markings.

On January 14 sigmoidoscopy was repeated, and the nodules for the first time had a distinctly yellowish or whitish-yellow color, a narrow erythematous base being observed in some of them. With the use of a more suitable biopsy forceps one of the nodules was excised and examined microscopically in a drop of saline. Clusters of ova of *Schistosoma japonicum* were seen. Examination of the blood showed a red-cell count of 4,900,000, with a hemoglobin of 14 gm. (Sahli), and a white-cell count of 35,000, with 40 per cent eosinophils.

On January 15 a course of antimony potassium tartrate was begun. A fresh 1 per cent aqueous solution was prepared on each day of treatment and within ½ hour prior to injection, 0.5 gm. of the drug being dissolved in 50 cc. of sterile distilled water under aseptic precautions; no attempt was made to sterilize the solution after it had been prepared. From this solution the appropriate dose was withdrawn and incorporated in 1000 cc. of 5 per cent dextrose in physiologic saline, for slowness of injection and a reduction of local irritating effects. The drug was given on alternate days, beginning with 40 mg. (representing 4 cc. of the 1 per cent solution) and increasing the dose by 20 mg. each time until 140 mg. (14 cc.) had been reached; this dose was not exceeded for the remainder of the course. A total of 1.8 gm. was given in fifteen injections over a period of 31 days. It was considered advisable to postpone the twelfth injection because of rather severe upper abdominal pains on the preceding day. Instructions had been left with the nursing staff to discontinue the intravenous injections if nausea, vomiting, upper abdominal pain, a sense of constriction or pain in the chest, stiffness of the muscles, bradycardia or a drop in the blood pressure occurred. One and a half hours were allowed for the intravenous injection, and the patient was kept in bed for 1 hour after each treatment. Physical examinations were made daily, blood pressures were taken twice a day, the urine was examined every other day and electrocardiograms were taken once a week at another hospital. Fluids were forced to prevent possible kidney damage from the drug, and the intake and output were recorded. A high-carbohydrate, high-protein diet with added vitamins was given to guard against liver damage. No serious toxic reactions were observed.

Clinically, improvement began early. After the second injection the temperature became normal and remained so thereafter except for a transient elevation from an upper

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‡Reproductions of this and subsequent roentgenograms will be included in the reprints of this paper. — ED.

respiratory infection. The appetite improved gradually, and the weight lost in the early part of the illness was regained. Only one positive stool was reported, and this was obtained on the day after the first dose of antimony potassium tartrate. On this occasion numerous ova were seen, consisting generally of mature forms containing actively motile miracidia. The spleen and liver were no longer palpable after January 29. A chest plate on February 16 showed less infiltration in both lung fields, although the hilar markings were still accentuated to the same extent as before. The white-cell counts on January 26 and 29 were respectively 20,550, with 40 per cent eosinophils, and 11,000, with 43 per cent eosinophils, whereas on February 4, 8 and 14 they were 9000, with 60 per cent eosinophils, 12,800, with 31 per cent eosinophils, and 7300, with 30 per cent eosinophils. Sigmoidoscopic evidences of improvement began as early as February 1, and by February 15 there was still further improvement, so that the nodules might readily have been missed had their previous location not been known. On February 16 the patient was transferred, greatly improved, to a general hospital for evacuation to the United States.

Discussion

Several features of this case deserve comment. In the first place, the failure of laboratory tests to demonstrate ova in the stools is not infrequent, in spite of refined concentration technics. Only one positive stool specimen was obtained during the patient's hospitalization, and that on the day following the first dose of antimony potassium tartrate, when the stool became heavily laden with ova. This may have been simple coincidence, but was more probably due to the provocative action of the drug on the gravid female worms, causing them to expel their eggs at one time. A somewhat analogous reaction is seen in malarial infections, in which the blood smear may not become positive until after a dose of quinacrine (Atabrine), when a heavy infection may become manifest.

Sigmoidoscopy has received attention as providing valuable diagnostic aid following a report by Johnson and Berry[5] that yellowish nodules of the upper rectal and rectosigmoid mucosa were characteristic of Asiatic schistosomiasis. From these nodules or pseudotubercles, which occur singly or in clusters, nests of ova can be removed with a simple biopsy forceps. Although we were aware of this diagnostic feature the diagnosis was not made because at first no pseudotubercles could be found and subsequently small, red macules and elevated lesions were observed from which no ova could be obtained. So far as we know, this is the first reference to the initial appearance of the yellow nodules of Johnson and Berry; with the lapse of eleven days, however, there was no mistaking their nature — the greater elevation, sense of firmness to the lip of the sigmoidoscope and yellowish color were all characteristic, and biopsy findings at this stage were merely confirmatory.

The serial roentgenograms of the chest were also interesting. Such films are not in themselves pathognomonic, presenting the picture of bronchopneumonia, but their association with urticaria, angioneurotic edema, leukocytosis, eosinophilia, fever and abdominal pain with liver tenderness should be considered strongly suggestive of schistosomiasis and should point to the advisability of repeated examinations of the stools and sigmoidoscopy. The pulmonary infiltrations have a doubtful pathogenesis. It is not known whether the roentgenologic picture represents a reaction of the lung parenchyma to ova transported from the mesenteric venules via the portal circulation and liver or to adult worms living in the lungs or to their ova deposited there. In fatal cases of Egyptian schistosomiasis with pulmonary involvement, adult worms have been found in the arteries of the lungs. It would not be at all surprising if adult worms of *S. japonicum* also develop in the lungs and that the eggs when present are the product of the worms located there. In this respect it is interesting to note that the same problem arises to explain the nature of cerebral schistosomiasis, in which ova have thus far been found only in the brain substance, with no evidence of the presence of adult worms.[6]

Attention is called to the complete lack of effect of 0.4 gm. of emetine given for six days. The drug was administered because of the possibility that some of the symptoms were due to an amebic hepatitis, although it was not expected to be of great value. Older authorities had stated that the drug had some schistosomicidal effect, but none was demonstrated with the small amount used in this patient. In marked contrast was the gratifying symptomatic and objective response to antimony potassium tartrate. Although two potential myocardial depressants were used in this case, no evidences of cardiac damage were detected.

Summary

An early case of Asiatic schistosomiasis is reported.

The characteristic yellowish nodules of the rectosigmoid and upper rectum were shown to have an earlier stage in which they have a distinctly red color and are smaller and less resistant to the sigmoidoscope than they are in the later course of their development. The diagnostic value of sigmoidoscopy is confirmed.

Serial roentgenologic findings are presented that may have represented a reaction of the lung parenchyma to ova or adult worms of *Schistosoma japonicum*.

The effectiveness of antimony potassium tartrate (tartar emetic) in this case was demonstrated.

References

1. Billings, F. T., Winkenwerder, W. L., and Hunninen, A. V. Studies on acute schistosomiasis japonica in Philippine Islands. I. Clinical study of 337 cases with preliminary report on results of treatment with fuadin in 110 cases. *Bull. Johns Hopkins Hosp.* 78:21-56, 1946.
2. Thomas, H. M., Jr., and Gage, D. P. Symptomatology of early schistosomiasis japonica. *Bull. U. S. Army M. Dept.* 4:197-202, 1945.
3. Faust, E. C., Wright, W. H., McMullen, D. B., and Hunter, G. W. Diagnosis of schistosomiasis japonica. I. Symptoms, signs and physical findings of schistosomiasis japonica at different stages in development of disease. *Am. J. Trop. Med.* 26:87-112, 1946.
4. Schistosomiasis japonica. *Bull. U. S. Army M. Dept.* 4:273-276, 1945.
5. Johnson, A. S., Jr., and Berry, M. G. Aid in recognition of schistosomiasis japonica. *Bull. U. S. Army M. Dept.* 4:125, 1945.
6. Carroll, D. G. Cerebral involvement in schistosomiasis japonica. *Bull. Johns Hopkins Hosp.* 78:219-234, 1946.

MEDICAL PROGRESS

THE PHYSIOLOGIC AND CLINICAL SIGNIFICANCE OF PLASMA PROTEINS AND PROTEIN METABOLITES*

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PROTEIN is an essential component of protoplasm. Both structure and function of body tissues are dependent on specific proteins, such as enzymes and hormones. Fluid balance, hemostasis, many hormone and lipoprotein complexes and certain immune mechanisms are related to protein nutrition. Recent observations derived from many sources have re-emphasized and extended the clinical significance of plasma proteins, protein metabolites and protein degradation products. The concept of constant interchange or "dynamic equilibrium" between the proteins of blood and other tissues,[1, 2] the elucidation of indispensable amino acids,[3, 4] the application of heavy nitrogen and marked carbon to problems of nitrogen metabolism and immunology[5–7] and the adaptation of physicochemical technics — for example, electrophoresis — and fractionation procedures to plasma proteins[8–11] are fundamental contributions to better clinical understanding of plasma protein significance. The significance, characterization and function of various circulating plasma proteins and protein metabolites, the evaluation of protein abnormalities and the general interrelations of amino acids, protein synthesis and nitrogen metabolism are considered in this paper.

CIRCULATING PROTEINS

The modern technic of electrophoresis, as developed by Tiselius,[8] affords a means of characterizing plasma proteins. This procedure depends on the application of an external electric field of force to charged protein molecules dissolved in a suitable solvent. Under such conditions, proteins move in one direction in acid solutions and in the opposite direction in alkaline solutions. Thus, in an apparatus providing a given electromotive field strength acting on proteins dispersed in a salt solution, movement of the protein is determined by its physical properties and the hydrogen ion concentration, the molar concentration and the nature of the solvent. Since different components of a protein aggregate usually move with different velocities, it is possible to distinguish several components within a complex protein aggregate such as plasma. Specialized refractometric optical systems, which project a shadow (*Schlieren*) pattern of the migrating protein on a photographic screen, afford a permanent record of electrophoretic mobility. Both the characteristic rate of motion, which determines the probable protein component, and the apparent relative concentration of that component may be calculated from the *Schlieren* pattern.[12]

Analyses of human plasma by modifications of this method have postulated at least six electrophoretic components: albumin, alpha-1, alpha-2, beta and gamma globulin and fibrinogen[12–16] (Fig. 1). Fractionation studies have indicated their distribution in plasma (Table 1). The conventional sodium sulfate "salting out" method of Howe,[21] which precipitates fibrinogen euglobulin and pseudoglobulins I and II at increasing molar concentrations, affords a somewhat different distribution (Table 1). Similarly, other methods, including ultracentrifugal sedimentation, osmotic pressure and viscosity, that depend on heterogeneous physical and chemical properties of protein, such as size, shape and electrical charge, provide diverse plasma protein distributions. Determination of plasma protein components by electrophoresis differs from the more familiar chemical method in yielding more complete fractional resolution, which particularly minimizes the overlap of albumin and the various globulins. Sodium sulfate fractionation, for example, appears to assign approximately 5 per cent more nitrogen (31 per cent more protein) to the albumin fraction than indicated by electrophoretic technics.[22] Accordingly, electrophoretic albumin-globulin ratios tend to be lower (about 30 per cent) than the chemically determined equivalent.[16] The more precise data from electrophoretic analyses of plasma should provide a supplemental, somewhat more readily interpreted, body of experimental and clinical findings. Extensive data derived from electrophoretic analyses of plasma in health and disease are rapidly becoming available.

Alterations in plasma protein concentration with age, sex, race, health and disease are well known. Normal ranges[18, 19, 23, 24] are denoted in Table 2. Deviation from these values occurs in many diseases. Hypoproteinemia, usually reflecting a depletion of the albumin fraction, is more frequent clinically than hyperproteinemia, which usually represents

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an increase in one or several of the globulin components of plasma. Diseases in which hypoproteinemia or hyperproteinemia may occur are listed in Table 3.

The clinical significance attending alterations in each of the various plasma protein fractions is not completely clear. Some pertinent observations, however, have been made.

Serum albumin is the most important circulating protein for maintenance of colloid osmotic (oncotic) pressure of the blood. Constituting approximately 55 to 60 per cent* of plasma protein, it is responsible for about 80 per cent of the oncotic pressure.[27] Its small size (molecular weight, 70,000) and relatively larger net charge account for an osmotic effect greater than that exerted by combinations of the various globulins (molecular weight, approximately 170,000 to 180,000). Serum albumin apparently attains maximal (adult) concentration at approximately one year of age[18, 24]; electrophoretically observed albumin concentrations of maternal and fetal plasmas, however, appear to be similar.[28] The quantity of circulating protein, including albumin, appears to increase in relation to plasma volume and surface area until maximal values are approximated coincident with puberty (see Tables 2 and 5). Decreased serum albumin is most frequently the result of protein loss by leakage into extravascular spaces (trauma or shock, or both) into urine (nephrosis, chronic glomerulonephritis and so forth) or from wound surfaces (hemorrhage and burns); inadequate protein synthesis associated with extensive liver damage (cirrhosis or hepatitis) or altered hepatic function (concomitant to severe anemia, chronic nephritides, various infections and so forth); inadequate dietary protein intake; and increased utilization or decreased absorption of protein. Increased protein utilization occurs when metabolism requires burning of protein for energy if supplies of carbohydrate and fat are inadequate to support caloric needs. This may ensue when parenteral amino acids, plasma and electrolyte replacement therapy are administered without supplying caloric requirements in the form of glucose or fat, when increased protein and caloric demands are not met in various acute and chronic diseases, such as typhoid fever, hepatitis, tuberculosis and hyperthyroidism, or

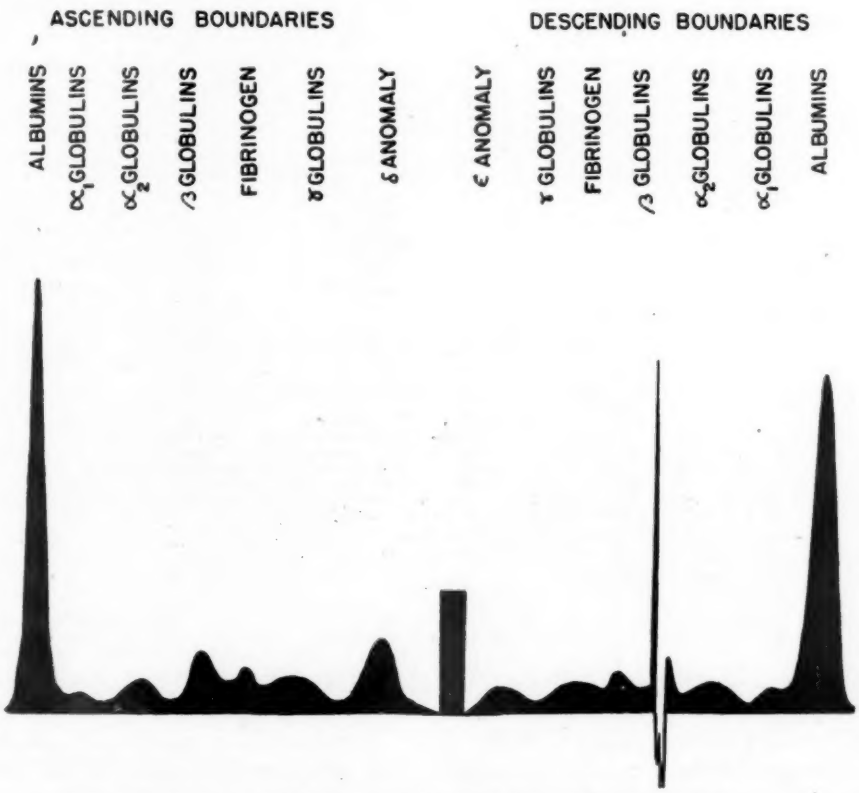

FIGURE 1. *A Typical Electrophoretic Pattern of Human Plasma.*
This diagram was derived from analysis of a 2 per cent solution of pooled normal human plasma in a sodium diethyl barbiturate buffer (pH 8.6) and an ionic strength of 0.1. It was kindly furnished by Dr. S. H. Armstrong, Jr., of the Department of Physical Chemistry, Harvard University.

*Present estimates are somewhat lower: 52 to 55 per cent.

when the heightened metabolic demands of rapid growth, pregnancy and lactation are confronted with relative protein and caloric inadequacy. Decreased absorption of protein is primarily associated with gastrointestinal abnormalities, including diarrhea, specific mucosal or intestinal vascular disease and surgical stomas of the small bowel.

Depletion of plasma protein, — specifically, albumin, — usually associated with a decreased plasma volume, probably represents a much more extensive depletion of tissue protein.[1, 34, 35] Thus, reversal of hypoalbuminemia with associated replenishment of tissue protein understandably requires considerable quantities of protein or albumin. With sufficient reduction of serum albumin and resultant diminution of plasma oncotic pressure, edema is likely to occur. The occurrence of edema, however, is modified by hydration, electrolyte (particularly sodium) concentration, tissue pressure, lymph flow, capillary permeability, extracellular fluid pressure, adrenocortical and gonadotropic hormones and so forth. It has been stated that the critical plasma concentrations below which edema occurs is approximated by a total protein of 5.5 gm. per 100 cc., an albumin level of 2.5 gm. per 100 cc. and a plasma specific gravity of 1.023.[35] Clinical aberrations from this observation are numerous, as might be expected, since protein concentration measurements afford an inadequate indication of the oncotic effect exerted by the total circulating protein and many associated factors further modify the occurrence of clinical edema. Recent evidence questions the validity of Starling's generally accepted oncotic equilibrium theory and suggests the inadequacy of a simple hypoproteinemic causation of such a well known clinical entity as famine edema.[36]

The albumin fraction appears to serve other functions of clinical interest. Partial binding of the sulfonamide drugs to albumin may account for their distribution in body fluids, solubility in plasma and decreased bacteriostatic activity.[37] The dye T-1824, used in the clinical determination of blood volume, is bound by albumin and migrates with it in the electrophoretic field. Its disappearance from plasma appears to be related to the rate at which albumin escapes.[38] It has been reported that normal or abnormally occurring albumin fractions may inhibit the colloidal gold reaction,[39, 40] cephalin-cholesterol flocculation[41] and sedimentation rate.[42] Subsequent unpublished data on fractionation have put these activities in small alpha-1 globulin impurities.[43]

Albumin, as a product of plasma fractionation, has considerable clinical value in the therapy of hemorrhagic, traumatic or burn shock.[44–46] It is chiefly useful in rapidly restoring the diminished plasma volume toward normal at the expense of extravascular fluids.[47] Albumin has also seemed efficacious in the treatment of severe malnutritional hypoproteinemia occurring in adults[44] and infants,[48] in nephritis[17, 49] and in cirrhosis.[50]

Hyperproteinemia, not the result of decreased plasma volume, is usually synonymous with hyperglobulinemia — an increase in one or several globulin fractions. Extensive data pertaining to alterations in the various electrophoretic globulin fractions are not yet available. Globulins have been reported to attain maximal (adult) concentrations by the fourth year of life.[18] Alpha-1 globulin may be closely associated clinically with the electrophoretically appositional albumin, since it appears to exert a similar effect on oncotic pressure[51] and to resemble albumin in its plasma clearance.[49] Alpha-1 and alpha-2

TABLE 1. *Distribution of Human Plasma Protein Components in Normal Adults as Determined by Electrophoretic and Sodium Sulfate Fractionation.*

Electrophoretic Fractionation*			Sodium Sulfate Fractionation		
Component	Percentage of total protein†	Concentration	Component	Percentage of total protein†	Concentration‡
		gm./100 cc.			*gm./100 cc.*
Total protein		6.03–6.72	Total protein		6.0–8.0
Albumin	55	3.32–4.04	Albumin	67	4.3–5.0
Globulin:					
Alpha-1	5	0.31–0.32	Pseudoglobulin II	7	0.2–0.8§
Alpha-2	9	0.48–0.52			
Beta	13	0.78–0.81	Pseudoglobulin I	19	0.8–1.9§
Gamma	11	0.66–0.74	Euglobulin	4	0.1–0.4§
Fibrinogen	7	0.34–0.43	Fibrinogen	3	0.17–0.25
Total	45	2.71–2.72	Total globulin	33	1.9–3.3

*The distribution of components in normal pooled human plasma as derived from electrophoretic analysis is based on the total refractive increment contributed by each component. The quantitative amount of each fraction is based on nitrogen analysis assuming the conventional conversion factor of 6.25. A further assumption tentatively assigns a similar refractive increment per gram of nitrogen to all components.[11] Data derived from several studies.[9, 11, 16, 17] Fractionation in diethylbarbiturate buffer at pH 8.6.

†Percentage of total protein represents an approximation.

‡Data derived largely from Trevorrow et al.[18] and Milam.[19]

§Data from Cantarow and Trumper.[20]

globulins occur in lower concentrations in fetal than in maternal plasmas.[28] Increased alpha globulins have been reported in a variety of diseases.[17, 49, 50, 52–55] The significance of these observations is unknown. It has been suggested that the depletion of plasma albumin may be reflected by a compensatory increase of alpha globulin in liver disease,[52] malnutrition, tuberculosis and carcinoma[56] or, conversely, that hyperglobulinemia prompts an equilibratory fall in albumin.[57]

Beta globulins are carriers of lipoid components and, with the alpha globulins, constitute the lipoproteins of plasma.[12, 58] Approximately two thirds of the total plasma cholesterol appears to be associated with beta globulin. Over half the carotene and phospholipids are also concentrated with the alpha and beta globulin fractions. Prothrombin appears to be a beta globulin.[12] The thymol-turbidity reaction appears to be related to alpha and beta globulins.[41]

Demonstrable increases in beta-globulin components of plasma have been reported in association with several diseases[13, 14, 17, 49, 50, 52–56, 58–61] and in maternal plasma at parturition.[28] The observed increase appears to depend on abnormally large amounts of lipoids, which migrate with the beta and alpha fractions. The refractometric error introduced by the plasma lipoids in such diseases subjects calculation of the plasma concentration of a given electrophoretic protein component to considerable error.[50]

Relatively purified plasma fractions composed largely of beta and gamma globulins have been prepared as specific isohemagglutinins with anti-A and anti-B activity.[62] These fractions have been found clinically acceptable as standardized blood-grouping serums.[63]

Since immunologic mechanisms are partially dependent on antibody response and many antibodies are related to gamma globulin, considerable interest has centered about electrophoretic demonstrations of relative changes in the gamma-globulin fraction of plasma. Antibodies reacting with diphtheria toxin, streptococcal erythrogenic toxin, influenza A virus, mumps virus and the H antigen of *Eberthella typhosa* have been immunologically demonstrated in the gamma-globulin fraction.[64] The concentration of these antibodies was some fifteen to thirty times that in pooled plasma. All antibodies, however, are not contained in the gamma-globulin fraction of plasma. The 0 antibody of *E. typhosa*, for example, appears to be associated electrophoretically with beta and possibly alpha, as well as with gamma globulin. Similarly, all gamma globulin is not antibody.[65] The presence of antibodies[66] and normal serum gamma globulin in lymphocytes[67] indirectly supports the concept of the extrahepatic origin of globulin. Antibody release from lymphocytes, attended by an increased serum gamma globulin, may be mediated through pituitary-adrenocortical control.[68]

TABLE 2. *Normal Plasma Protein Concentration Values from Birth to Maturity.*

AGE*	PLASMA PROTEIN†			
	TOTAL PROTEIN gm./100 cc.	ALBUMIN‡ gm./100 cc.	GLOBULIN gm./100 cc.	FIBRINOGEN gm./100 cc.
Premature infants[24]	4.55 ± 0.59	3.55 ± 0.65	1.01 ± 0.45	0.27 ± 0.15
Full-term infants[18, 24]...	5.11 ± 0.76	3.76 ± 0.43	1.34 ± 0.41	0.24 ± 0.04
	to	to	to	to
	5.70 ± 0.45	3.79 ± 0.33	1.66 ± 0.29	0.23 ± —
Birth to 1 year[24]	6.10 ± 0.29	4.97 ± 0.73§	1.38 ± 0.68	0.28 ± 0.08§
1–4 years[18].....	6.94 ± 0.47§	4.59 ± 0.31	2.03 ± 0.34§	0.21 ± 0.06
		to		
		4.83 ± 0.30		
5–12 years[24]	7.30 ± 0.59	5.0 ± 0.78	2.4 ± 0.74	0.28 ± 0.04
Under 15 years[19]	7.16	4.72	2.49	Included with globulin
Adults[18, 19].....	7.18 ± 0.013	4.59 ± 0.011	2.54 ± 0.13	—
	to	to	to	
	6.94 ± 0.47	4.70 ± 0.32	2.03 ± 0.34	0.21 ± 0.06
Adult range (95 per cent)[19]	6.3 – 8.0	3.9 – 5.3	1.3 – 3.4	Included with globulin

*No significant variation with sex, but some racial variation.

†Values obtained are somewhat variable, depending on technic of determination. Most of the reported total protein values are derived from micro-Kjeldahl analyses, and the albumin and globulin, from sodium sulfate fractionation.

‡Albumin may vary somewhat with the season. The variation may be a manifestation of seasonal blood-volume changes.[18]

§Indicates mature level attained.

Clinical evidence pertaining to the change in gamma globulin is somewhat less striking than inference from immunologic data suggests. In relation to infant immunity it is interesting that the gamma-globulin concentration of fetal plasma, determined from placental blood at birth, is considerably greater than that occurring in the parenteral maternal plasma.[28] Gamma globulin has been to that of gamma globulin.[70] Gamma globulin may be diminished in chronic malnutrition associated with hypoproteinemia.[56, 71] This observation is particularly interesting in view of the possible relation of protein deficiency to impaired antibody production.[72] Gamma globulin appears to be largely responsible for positive colloidal gold and cephalin-flocculation tests.[40] It has no effect on the thymol-

TABLE 3. *Conditions Associated with Alterations in Plasma Protein Concentration.**

HIGH CONCENTRATIONS	LOW CONCENTRATIONS
General	*General*
Usually associated with dehydration and with increased globulin, which are frequent in diseases of reticuloendothelial system and in chronic infections	Usually associated with mechanical loss of protein by extravasation or renal excretion or with decreased albumin formation as result of malnutrition or liver disease
Specific	*Specific*
Dehydration:	Physical loss of plasma proteins from circulation:
Insufficient fluid intake	Hemorrhage, acute or chronic, and blood dyscrasias
Fluid loss	Weeping wounds or skin lesions (burns)
Intestinal obstruction and fistulas	Shock, surgical and traumatic
Diarrhea, especially in infants, and also cholera and dysentery	Kidney disease with albuminuria:
Vomiting	Nephrosis
Severe diabetic acidosis	Chronic glomerulonephritis
Intense heat and exertion	Amyloidosis
Addison's disease	
Shock, surgical and traumatic	Malnutrition (low albumin):
Burns, first few hours (in some cases)	Dietary inadequacy in chronic infections
Fulminant infections	Low-protein diet
	Incomplete absorption, as in sprue and celiac syndrome
Diseases involving reticuloendothelial system (high globulin):	Cancer of stomach and pancreas
Multiple myeloma	Pernicious anemia
Leukemia	Diabetes mellitus, unregulated
Liver cirrhosis and cancer	Hyperthyroidism
Acute hepatitis	Toxemias of pregnancy
Chronic infections (high globulin):	Conditions with retarded albumin synthesis, presumably because of liver damage (low albumin):
Acute nephritis	Cirrhosis and cancer of liver
Ulcerative tuberculosis	Chronic poisoning (benzene, phosphorus and so forth)
Syphilis	Hepatitis, chronic
Lymphopathia venereum	Hepatorenal syndrome
Subacute bacterial endocarditis	
Acute disseminated lupus erythematosus	
Periarteritis nodosa	
Rheumatic fever	
Rheumatoid arthritis	
Boeck's sarcoid	
Leprosy	
Kala-azar	
Schistosomiasis	
Filariasis	
Trypanosomiasis	
Chronic suppurative infections:	
Pyelonephritis	
Pyonephrosis	
Gangrene associated with diabetes mellitus	
Malaria	
Tuberculosis	

*Modified from Kagan[25] and from Phillips et al.[26]

reported as increased in scarlet fever — the increase appearing to be associated with increased titer of antistreptolysin O[54] — and in relapsing malarial infection with *Plasmodium vivax* associated with paroxysms.[53] An increase in this fraction has also been noted in association with acute nephritis, acute rheumatic fever, periarteritis nodosa,[17, 55] lupus erythematosus[69] and various subacute and chronic infections.[55] A nonspecific increase in gamma globulin has been observed in various types of myeloma[13, 55] and chronic hepatic disease.[50, 52, 55] The Wassermann antibody appears to be associated with the gamma-globulin fraction, having an electrophoretic mobility between beta and gamma components and a sedimentation constant similar turbidity reaction,[41] and may inhibit the sedimentation rate,[42] although in particular cases an accelerated sedimentation rate is apparently related to gamma-globulin increase.[55]

The clinical administration of relatively purified gamma globulin has proved efficacious in the prevention and attenuation of measles[73, 74] and in the prophylaxis of infectious hepatitis[75, 76] and mumps orchitis (if the gamma globulin is derived from mumps convalescent serums).[77]

Fibrinogen, the last of the currently isolated major plasma protein components, appears to undergo little fluctuation with growth and health.[19] It is primarily concerned with the blood-clotting mechanism. Fibrin has been isolated, purified and

adapted to clinical use.[9, 12] Fibrinogen concentrations may be increased in a variety of conditions: acute infections, malaria, pregnancy and menstruation and following roentgen irradiation,[78] nephrosis and cirrhosis.[17, 50, 55] Presumably, a relatively large proportion of protein having an electrophoretic mobility similar to fibrinogen is a beta globulin not specifically related to the blood-clotting function.[11] The sedimentation rate of erythrocytes may be related to fibrinogen,[42] presumably being proportional to the amount of so-called "contractinogen" it contains.[79] Recent evidence, however, suggests that the elevated sedimentation rate occurring in many conditions may also be related to one or several of the globulin fractions.[55] Decreased plasma fibrinogen has been reported in association with several diseases, but normal concentrations are low and variations are large; hence, the deviations are difficult to interpret. Sodium sulfate precipitation of fibrinogen, generally used, may precipitate some of the fibrinogen with globulin and may further impair interpretation.[18] Reported physiologic functions of the plasma protein components and electrophoretic variations occurring in association with several diseases are summarized in Table 4.

Observations pertaining to pathologic variations in albumin and globulin have repeatedly indicated that numerical expression of the albumin-globulin

TABLE 4. *Characterization, Known Physiologic Function and Reported Electrophoretic Variations with Disease of the Major Plasma Protein Components.**

DATA	ALBUMIN	ALPHA GLOBULINS	BETA GLOBULIN	GAMMA GLOBULIN	FIBRINOGEN
Occurrence in plasma fractions†	Fraction V (98.5–100%)	Fraction IV (64%) Fraction III (21%)	Fraction III (61%) Fraction IV (31%)	Fraction II (98–99%)	Fraction I (62%)
Other known factors in fraction†		Iron-binding globulin, serum esterase, hypertensinogen, vitamin A, carotenoids, cholesterol, phosphatides, estrogens, isoagglutinins, complement C‡; luteinizing, follicle stimulating and thyrotropic hormones, protein-bound iodine and alkaline phosphatase			Antihemophilic globulin
Known physiologic function	Maintains oncotic pressure of blood; maintains plasma volume; binds sulfonamide and dye T–1824; inhibits sedimentation rate of red cells.	Constitute lipoproteins of plasma Alpha-1 globulin has oncotic effect and plasma clearance similar to that of albumin; impurities associated with it appear to inhibit cephalin-cholesterol and colloidal gold flocculation.	Principal component of Bence-Jones protein; largely responsible for thymol-flocculation reaction; related to prothrombin.	Comprises antibodies for diphtheria toxin, streptococcus erythrogenic toxin and influenza A virus and H antigen of *E. typhosa*; associated with Wassermann antibody; occurs in lymphocytes; largely responsible for colloidal gold and cephalin-flocculation reactions; inhibits sedimentation rate of red cells.	Fibrinogen in blood-coagulation mechanism; largely responsible for rapid sedimentation rate of red cells.
Reported alterations in several diseases:					
Increased		Nephrosis§ Cirrhosis§ Arsenical hepatitis with low albumin§ Scarlet fever Malnutrition Tuberculosis§ Diabetes mellitus	Nephrotic syndrome Cirrhosis Metastatic carcinoma of liver Multiple myeloma May be associated with increased serum cholesterol	Normal fetal plasma Cirrhosis Multiple myeloma Acute nephritis Periarteritis nodosa Lupus erythematosus Relapsing (*P. vivax*) malaria Addison's disease Monocytic leukemia Acute rheumatic fever Associated with anti-streptolysin-O titer in scarlet fever.	Nephrosis Hepatic cirrhosis Relapsing *P. vivax* malaria Pregnancy
Decreased	Malnutrition, with hypoproteinemia Hepatic cirrhosis Extensive metastatic hepatic carcinoma Chronic glomerulonephritis, with albuminuria or nephrotic syndrome Relapsing *P. vivax* malaria Chronic tuberculosis			May be diminished in nephrotic syndrome Malnutrition with hypoproteinemia	

*Data pertaining to physiologic function and abnormal variations of the specific plasma protein components are, at present, quite limited. Subsequent data will undoubtedly extend, clarify or modify those indicated in this table.

†The concentration of the principal protein components in the various fractions, denoted as percentages, is derived largely from data of Cohn, Oncley, Strong, Hughes, and Armstrong[12] and subsequent reports from the Department of Physical Chemistry, Harvard Medical School. Fractions denoted by Roman numerals refer to that portion of the plasma protein precipitated from an alcohol-water solution of known concentration, ionic strength and pH at very low temperatures. The precipitates are subsequently dried, purified and analyzed for protein components by electrophoretic technics. Several electrophoretic components may be concentrated in any one fraction. Methods of fractionation have been modified to increase yields of albumin, gamma globulin, fibrinogen and so forth in a given fraction. Six major fractions (I–VI) and seven subfractions have been evolved by various procedures to date. Fractions II and III are precipitated together in several methods.

‡Many of the factors that appear to be concentrated in Fraction II plus III have not been specifically isolated or purified; others, as yet undemonstrated, may occur in these or other fractions.

§The increase is represented largely by alpha-2 globulin.

ratio provides little insight into specific alterations in albumin or globulin fractions.[18, 24, 25, 80] Used as a diagnostic aid, the ratio may be quite misleading: in nephrosis, a decreased albumin-globulin ratio is dependent on depleted albumin and probable, relative increases in alpha and beta globulins, and in cirrhosis, on depleted albumin, increased fibrinogen and gamma globulin; in malnutrition, it probably depends on depleted albumin and relatively increased alpha globulin; in pregnancy it may be dependent on hemodilution of albumin, with a relative increase in fibrinogen; and in chronic infections, it depends on an unchanged albumin and increased beta-globulin and gamma-globulin fractions. Albumin is synthesized principally in the liver, whereas globulin may be synthesized extrahepatically.[67, 81] The amino acid compositions of albumin, gamma globulin, beta globulin and fibrinogen differ.[82] Since the origin, structure and function of albumin and globulin differ and the various globulin fractions have further structural and functional differences, it is evident that these fractions, determined with total protein concentrations, should be considered individual variables. The albumin-globulin ratio, therefore, as generally used has little significance and frequently leads to confused clinical interpretations.

Hypoproteinemia and hyperproteinemia, by usage, refer to the quantity of protein dissolved in an arbitrary amount of plasma. Since the volume of circulating plasma is subject to considerable change in relation to growth, health and acute and chronic disease, it is evident that significant changes in quantities of circulating plasma protein may be masked if the protein concentration is measured without regard for expanding or contracting blood volume.[34, 83–86] Thus, a protein concentration of 6 gm. per 100 cc. in a patient with a total plasma volume of 2000 cc. represents a significantly different amount of circulating protein than that occurring in another person of similar size, also with a total protein of 6 gm. per 100 cc. but a plasma volume of 1000 cc. Such a hypothetical case indicates a difference of 60 gm. (50 per cent) in the total circulating plasma protein. This difference is masked by the relatively unphysiologic consideration of concentration alone — for as Peters[80] has pointed out, a three-dimensional function cannot be evaluated by two-dimensional measurements, and alterations in total circulating protein and plasma volume cannot be estimated accurately from total protein concentrations.[85, 86]

Plasma-volume alterations are not static phenomena. As a phase of the total extracellular compartment, plasma-volume change is subsequent to factors altering water balance. Changes in plasma volume have a temporal significance — for example, *relative* to the previously existing plasma volume in a given patient or *absolute* in regard to a previously normal plasma volume. Altered concentrations of circulating plasma components may be masked by either an increased or a decreased plasma volume. Plasma protein and electrolyte concentrations, therefore, may be more relative than absolute. An increased plasma volume is most frequently dependent on one or several factors: altered renal function or sodium retention, or both; increased plasma bicarbonate, with altered carbon dioxide and oxygen tensions, and an increased basal metabolic rate; and decreased circulating cell volume

TABLE 5. *Normal Plasma Volume* and Circulating Protein Values from Birth to Maturity.*

Age†	Plasma Volume			Circulating Protein‡	
	total	per kilogram	per square meter	total§	unit
yr.	*cc.*	*cc.*	*cc.*	*gm.*	*gm./unit of plasma volume*
Neonatal[29] ...	156 (144–164)	48 (44–55)	740 (660–800)	8 (7–10)	39 (35–43)
Under 1[29]	203 (144–270)	43 (28–55)	747 (600–940)	12 (8–18)	46 (37–58)
1–4[29]	577 (483–653)	41 (34–46)	942 (825–1020)	40 (34–46)	66 (57–71)
5–12[29]	1146 (891–1590)	41 (37–46)	1120 (1010–1230)	84 (65–116)	84 (74–90)
13–16[29]	2230 (2030–2610)	42 (34–52)	1450 (1195–1710)	160 (146–186)	104 (86–123)
17–89[30–33]	2800 (2300–3100)	44 (40–49)	1628 (1624–1680)	196 (162–220)	114 (113–118)

*As determined with azo dye T-1824 (Evans blue).

†All children within anthropometric norms.

‡Total circulating protein values derived from average plasma volume data and average plasma protein concentrations noted in Table 2; tabulated values are averages and do not include standard deviations.

§Total circulating protein = total protein (gm. per 100 cc.) ÷ 100 x total plasma volume (cc.).

and hemoglobin. Decreased plasma volume usually derives from several factors: increased sodium and chloride loss; decreased plasma bicarbonate, with altered carbon dioxide and oxygen tensions; albumin depletion; water and salt deprivation; severe fluid loss, with dehydration; and frank plasma loss. The first three factors primarily alter osmotic equilibriums; they may be associated with abnormal volume. A simple method of estimating blood volume from change in blood specific gravity following plasma infusion has been reported.[91]

It is to be hoped that consideration of the more fundamental concept of circulating proteins per unit of plasma volume will gradually supersede the often confusing two-dimensional measurement of plasma protein concentration. To this end, normal

TABLE 6. *Conditions Associated with Alterations in Plasma Volume.**

INCREASED PLASMA VOLUME	DECREASED PLASMA VOLUME
I. Conditions associated with altered renal function or sodium retention, or both:	I. Conditions associated with altered osmotic equilibriums that may be associated with altered renal function:
Cardiac insufficiency, with congestive failure (II),[92, 93] associated with decreased cardiac output[94] and increased venous pressure[92, 93, 95]	*a.* Increased sodium or chloride loss, or both:
Subacute or chronic glomerulonephritis when associated with edema, anemia and congestive failure (II)[96]	Chronic glomerulonephritis, with hypoalbuminemia without edema[96]
Excessive sodium intake (rare in normal persons[97])	Diarrhea, especially in infants (II)
Steroid hormone[98] and desoxycorticosterone administration[99]	Vomiting (II)[97, 103]
Hypertonic glucose administration (transient)	Excessive sweating (II)[97, 100, 103]
	Addison's disease, untreated (I*b*)[108, 109]
II. Conditions associated with increased bicarbonate, altered carbon dioxide and oxygen tensions or increased basal metabolic rate:	*b.* Decreased plasma bicarbonate, altered carbon dioxide and oxygen tensions and decreased basal metabolic rate:
Acute pneumococcal pneumonia[100, 101]	Pulmonary edema with infection[100]
Hyperthyroidism[102]	Fulminant pneumonia (IV)[100, 101]
Base administration[97, 100, 103]	Recovery phase of pneumonia[101] or congestive failure (I*a*)[92, 93] (relative decrease)
	Starvation with ketosis (I*c*)[97, 103]
	Diabetic acidosis (I*a*)[110]
	Myxedema[102]
	Acid-salt diuresis (I*a*)[97, 103]
III. Conditions associated with decreased circulating red-cell volume and hemoglobin (II)[104]:	*c.* Albumin depletion:
Secondary hypochromic anemia	Malnutrition, severe
Hemolytic anemia	Cirrhosis, with albumin depletion[50]
Macrocytic anemia of unknown etiology	II. Conditions associated with dehydration:
Pernicious anemia[105]	*a.* Water deprivation and salt depletion[97, 103, 111, 112]
Malaria without fever[106]	*b.* Severe fluid loss:
	Diabetes insipidus[97]
	Artificial fever (typhoid, diathermy, infrared) (II*a*)[113]
IV. Miscellaneous conditions:	III. Conditions associated with plasma and blood loss (IV):
Normal pregnancy (I)[107]	*a.* Acute hemorrhage[114, 115]
Lymphogranuloma inguinale[84]	Intestinal bleeding[33]
	Laceration of vessels[33]
	Skeletal trauma[33]
	b. Local plasma loss:[33]
	Burns
	Peritonitis
	IV. Conditions associated with peripheral vascular collapse:
	Malaria at fastigium[106]

*Blood volume is altered in many conditions. In some cases a variation in the total red-cell volume is more significant than alteration of plasma volume, as in chronic anemia and polycythemia. This table is confined to states in which plasma-volume changes have been observed and recently reported. Most frequently, several conditions concurrently occur to modify plasma volume. The resultant of these influences determines the direction of plasma-volume change. The groupings as tabulated, therefore, are resultant expressions of various influences. Accordingly, the various pathologic processes are somewhat inadequately tabulated under a single heading. When other associated conditions significantly modify the reported deviation, they are indicated by the appropriate ipsilateral Roman numeral or letter, or both, in parentheses.

renal function. Abnormal renal function may supervene, in association with peripheral vascular collapse.

Clinical measurements of the plasma volume are usually accomplished by injecting a given amount of an azo blue dye, T-1824, and determining the concentration (dilution) of dye in several plasma or serum samples obtained at stated intervals after injection. From these data, the plasma volume may be calculated.[87, 88] A simplified technic, employing injection of a fixed amount of dye with subsequent withdrawal and analysis of a single blood sample at a given time thereafter, has been reported.[89, 90] This modification provides a practicable clinical method for determining plasma values and an incomplete tabulation of plasma volume and circulating plasma protein variations in disease are offered in Tables 5 and 6 — correlative to Tables 2 and 3, respectively.

(To be concluded)

REFERENCES

1. Holman, R. L., Mahoney, E. B., and Whipple, G. H. Blood plasma protein given by vein utilized in body metabolism. II. Dynamic equilibrium between plasma and tissue proteins. *J. Exper. Med.* 59:269-282, 1934.
2. Madden, S. C., and Whipple, G. H. Plasma proteins: their source, production and utilization. *Physiol. Rev.* 20:194-217, 1940.
3. Rose, W. C. Nutritive significance of amino acids. *Physiol. Rev.* 18:109-136, 1938.
4. Rose, W. C. Role of protein in diet. *Proc. Inst. Med. Chicago* 15: 24, 1944.
5. Schoenheimer, R. *The Dynamic State of Body Constituents.* Harvard University Monographs in Medicine and Public Health, No. 3. 78 pp. Cambridge, Massachusetts: Harvard University Press, 1941.

6. Schoenheimer, R., Ratner, S., Rittenberg, D., and Heidelberger, M. Interaction of blood proteins of rat with dietary nitrogen. *J. Biol. Chem.* **144**:541-544, 1942.
7. Heidelberger, M., Trefers, H. P., Schoenheimer, R., Ratner, S., and Rittenberg, D. Behavior of antibody protein toward dietary nitrogen in active and passive immunity. *J. Biol. Chem.* **144**: 555-562, 1942.
8. Tiselius, A. New apparatus for electrophoretic analysis of colloidal mixtures. *Tr. Faraday Soc.* **33**:524, 1937.
9. Chemical, clinical, and immunological studies on products of human plasma fractionation. Chap. II-XIII. *J. Clin. Investigation* **23**: 433-601, 1944.
10. Cohn, E. J. Chemical separation and clinical appraisal of components of blood. *Medicine* **24**:333-338, 1945.
11. Cohn, E. J., Strong, L. E., Hughes, W. L., Jr., Mulford, D. J., Ashworth, J. N., Melin, M., and Taylor, H. L. Preparation and properties of serum and plasma proteins. IV. System for separation into fractions of protein and lipoprotein components of biological tissues and fluids. *J. Am. Chem. Soc.* **68**:459-475, 1946.
12. Cohn, E. J., Oncley, J. L., Strong, L. E., Hughes, W. L., Jr., and Armstrong, S. H., Jr. Chemical, clinical, and immunological studies on products of human plasma fractionation. I. Characterization of protein fractions of human plasma. *J. Clin. Investigation* **23**:417-432, 1944.
13. Longsworth, L. G., Shedlovsky, T., and MacInnes, D. A. Electrophoretic patterns of normal and pathological human blood serum and plasma. *J. Exper. Med.* **70**:339-413, 1939.
14. Luetscher, J. A., Jr. Electrophoretic analysis of plasma and urinary proteins. *J. Clin. Investigation* **19**:313-320, 1940.
15. Dole, V. P. Electrophoretic patterns of normal plasma. *J. Clin. Investigation* **23**:708-713, 1944.
16. Moore, D. H., and Lynn, J. Electrophoretic measurements on normal human plasma. *J. Biol. Chem.* **141**:819-825, 1941.
17. Thorn, G. W., Armstrong, S. H., Jr., Davenport, V. D., Woodruff, L. M., and Tyler, F. H. Chemical, clinical, and immunological studies on products of human plasma fractionation. XXX. Use of salt-poor concentrated human serum albumin solution in treatment of chronic Bright's disease. *J. Clin. Investigation* **24**:802-828, 1945.
18. Trevorrow, V., Kaser, M., Patterson, J. P., and Hill, R. M. Plasma albumin, globulin, and fibrinogen in healthy individuals from birth to adulthood. II. Normal values. *J. Lab. & Clin. Med.* **27**: 471-486, 1941.
19. Milam, D. F. Plasma protein levels in normal individuals. *J. Lab. & Clin. Med.* **31**:285-290, 1946.
20. Cantarow, A., and Trumper, M. *Clinical Biochemistry.* Third edition. 647 pp. Philadelphia: W. B. Saunders Company, 1945.
21. Howe, P. E. Use of sodium sulfate as globulin precipitant in determination of proteins in blood. *J. Biol. Chem.* **49**:93-107, 1921.
22. Taylor, H. L., and Keys, A. Fractionation of normal serum proteins by electrophoretic and sodium sulfate methods. *J. Biol. Chem.* **148**:379-381, 1943.
23. Myers, V. C., and Muntwyler, E. Chemical changes in blood and their clinical significance. *Physiol. Rev.* **20**:1-36, 1940.
24. Rapoport, M., Rubin, M. I., and Chaffee, D. Fractionation of serum and plasma proteins by salt precipitation in infants and children. I. Changes with maturity and age. II. Changes in glomerulonephritis. III. Changes in nephrosis. *J. Clin. Investigation* **22**:487-497, 1943.
25. Kagan, B. M. Clinical significance of serum proteins. *South. M. J.* **36**:234-238, 1943.
26. Phillips, R. A., Van Slyke, D. D., Dole, V. P., Emerson, K., Jr., Hamilton, P. B., and Archibald, R. M. Copper sulfate method for measuring specific gravities of whole blood and plasma. Monograph Publications, Josiah Macy, Jr., Foundation, 1945.
27. Cohn, E. J. Plasma proteins: their properties and functions. *Tr. & Stud., Coll. Physicians, Philadelphia* **10**:149-162, 1942.
28. Longsworth, L. G., Curtis, R. M., and Pembroke, R. H., Jr. Electrophoretic analysis of maternal and fetal plasmas and sera. *J. Clin. Investigation* **24**:46-53, 1945.
29. Brines, J. K., Gibson, J. G., 2d, and Kunkel, P. Blood volume in normal infants and children. *J. Pediat.* **18**:447-457, 1941.
30. Gibson, J. G., 2d, and Evans, W. A., Jr. Clinical studies of blood volume. II. Relation of plasma and total blood volume to venous pressure, blood velocity rate, physical measurements, age and sex in ninety normal humans. *J. Clin. Investigation* **16**:317-328, 1937.
31. Stewart, J. D., and Rourke, G. M. On measurement of extracellular fluid volume with thiocyanate and body fluid analyses in 33 normal individuals. *J. Lab. & Clin. Med.* **26**:1383-1387, 1941.
32. Davis, L. J. Determination of blood volume in man with Evans blue ("T-1824"). *Edinburgh M. J.* **49**:465-483, 1942.
33. Noble, R. P., and Gregersen, M. I. Blood volume in clinical shock. II. Extent and cause of blood volume reduction in traumatic, hemorrhagic, and burn shock. *J. Clin. Investigation* **25**:172-183, 1946.
34. Weech, A. A., Wollstein, M., and Goettsch, E. Nutritional edema in dog. V. Development of deficits in erythrocytes and hemoglobin on diet deficient in protein. *J. Clin. Investigation* **16**: 719-728, 1937.
35. Moore, N. S., and Van Slyke, D. D. Relationships between plasma specific gravity, plasma protein content and edema in nephritis. *J. Clin. Investigation* **8**:337-355, 1930.
36. Keys, A., Taylor, H. L., Mickelsen, O., and Henschel, A. Famine edema and mechanism of its formation. *Science* **103**:669, 1946.
37. Davis, B. D. Binding of sulfonamide drugs by plasma proteins. Factor in determining distribution of drugs in body. *J. Clin. Investigation* **22**:753-762, 1943.
38. Rawson, R. A. Binding of T-1824 and structurally related diazo dyes by plasma proteins. *Am. J. Physiol.* **138**:708-717, 1943.
39. Gray, S. J. Mechanism of colloidal gold reaction of blood serum in liver disease. *Proc. Soc. Exper. Biol. & Med.* **51**:400, 1942. Studies on mechanism of spinal fluid colloidal gold reaction. *Ibid.* **51**: 401, 1942.
40. Kabat, E. A., Hanger, F. M., Moore, D. H., and Landow, H. Relation of cephalin flocculation and colloidal gold reactions to serum proteins. *J. Clin. Investigation* **22**:563-568, 1943.
41. Recant, L., Chargaff, E., and Hanger, F. M. Comparison of cephalin-cholesterol flocculation with thymol turbidity test. *Proc. Soc. Exper. Biol. & Med.* **60**:245-247, 1945.
42. Gray, S. J., and Mitchell, E. B. Effect of purified protein fractions on sedimentation rate of erythrocytes. *Proc. Soc. Exper. Biol. & Med.* **51**:403, 1942.
43. Armstrong, S. H., Jr. Personal communication.
44. Janeway, C. A., Gibson, S. T., Woodruff, L. M., Heyle, J. T., Bailey, O. T., and Newhouser, L. R. Concentrated human serum albumin: albumin in treatment of shock: safety of albumin: albumin in treatment of hypoproteinemia. *J. Clin. Investigation* **23**:465-490, 1944.
45. Cournand, A., Noble, R. P., Breed, E. S., Lawson, H. D., Baldwin, E. DeF., Pinchot, G. B., and Richards, D. W., Jr. Clinical use of concentrated human serum albumin in shock, and comparison with whole blood and with rapid saline infusion. *J. Clin. Investigation* **23**:491-505, 1944.
46. Warren, J. V., Stead, E. A., Jr., Merrill, A. J., and Brannon, E. S. Treatment of shock with concentrated human serum albumin: preliminary report. *J. Clin. Investigation* **23**:506-509, 1944.
47. Heyl, J. T., Gibson, J. G., 2d, and Janeway, C. A. Studies on plasma proteins. V. Effect of concentrated solutions of human and bovine serum albumin on blood volume after acute blood loss in man. *J. Clin. Investigation* **22**:763-773, 1943.
48. Metcoff, J. Unpublished data.
49. Luetscher, J. A., Jr. Effect of single injection of concentrated human serum albumin on circulating proteins and proteinuria in nephrosis. *J. Clin. Investigation* **23**:365-371, 1944.
50. Thorn, G. W., Armstrong, S. H., Jr., and Davenport, V. D. Chemical, clinical, and immunological studies on products of human plasma fractionation. XXXI. Use of salt-poor concentrated human serum albumin solution in treatment of hepatic cirrhosis. *J. Clin. Investigation* **25**:304-323, 1946.
51. Oncley, J. L., Scatchard, G., and Brown, A. Physical chemical characteristics of certain of proteins of normal human plasma. *J. Physical Chem.* (in press).
52. Gray, S. J., and Barron, E. S. G. Electrophoretic analyses of serum proteins in diseases of liver. *J. Clin. Investigation* **22**:191-200, 1943.
53. Dole, V. P., and Emerson, K., Jr. Electrophoretic changes in plasma protein patterns of patients with relapsing malaria. *J. Clin. Investigation* **24**:644-647, 1945.
54. Dole, V. P., Watson, R. F., and Rothbard, S. Electrophoretic changes in serum protein patterns of patients with scarlet fever and rheumatic fever. *J. Clin. Investigation* **24**:648-656, 1945.
55. Malmros, H., and Blix, G. Plasma proteins in cases with high sedimentation rates. *Acta med. Scandinav.* Supp. **170**:280-306, 1946.
56. Chow, B. F. Electrophoretic studies on effect of protein depletion on plasma proteins and regeneration of plasma proteins after oral administration of hydrolysates prepared from casein and lactalbumin. New York Acad. of Sc. Conference on Protein Hydrolysates, December, 1945.
57. Bjorneboe, M. Serum proteins during immunization. *Acta path. et microbiol. Scandinav.* **20**:221, 1943.
58. Longsworth, L. G., and MacInnes, D. A. Electrophoretic study of nephrotic sera and urine. *J. Exper. Med.* **71**:77-82, 1940.
59. Moore, D. H., Kabat, E. A., and Gutman, A. B. Bence-Jones proteinemia in multiple myeloma. *J. Clin. Investigation* **22**:67-75, 1943.
60. Blackman, S. S., Jr., Barker, W. H., Buell, M. V., and Davis, B. D. On pathogenesis of renal failure associated with multiple myeloma. Electrophoretic and chemical analysis of protein in urine and blood serum. *J. Clin. Investigation* **23**:163-166, 1944.
61. Lewis, L. A., Schneider, R. W., and McCullagh, E. P. Tiselius electrophoresis studies of plasma proteins in diabetes mellitus. *J. Clin. Endocrinol.* **4**:535-539, 1944.
62. Pillemer, L., Oncley, J. L., Melin, M., Elliott, J., and Hutchinson, M. C. Separation and concentration of isohemagglutinins from group-specific human plasma. *J. Clin. Investigation* **23**:550-553, 1944.
63. DeGowin, E. L. Appraisal of isohemagglutinin activity. *J. Clin. Investigation* **23**:554-556, 1944.
64. Enders, J. F. Concentrations of certain antibodies in globulin fractions derived from human blood plasma. *J. Clin. Investigation* **23**: 510-530, 1944.
65. Kabat, E. A. Immunochemistry of proteins. *J. Immunol.* **47**:513-587, 1943.
66. Dougherty, T. F., Chase, J. H., and White, A. Demonstration of antibodies in lymphocytes. *Proc. Soc. Exper. Biol. & Med.* **57**: 295-298, 1944.
67. Kass, E. H. Occurrence of normal serum gamma-globulin in human lymphocytes. *Science* **101**:337, 1945.
68. Dougherty, T. F., Chase, J. H., and White, A. Pituitary-adrenal cortical control of antibody release from lymphocytes. Explanation of amnestic response. *Proc. Soc. Exper. Biol. & Med.* **58**:135-140, 1945.
69. Coburn, A. F., and Moore, D. H. Plasma proteins in disseminated lupus erythematosus. *Bull. Johns Hopkins Hosp.* **73**:196-221, 1943.
70. Davis, B. D., Moore, D. H., Kabat, E. A., and Harris, A. Electrophoretic, ultracentrifugal, and immunochemical studies on Wassermann antibody. *J. Immunol.* **50**:1-20, 1945.
71. Krebbs, E. G. Depression of gamma globulin in hypoproteinemia due to malnutrition. *J. Lab. & Clin. Med.* **31**:85-89, 1946.
72. Cannon, P. R., Chase, W. E., and Wissler, R. W. Relationship of protein reserves to antibody production. I. Effects of low-protein diet and of plasmaphoresis upon formation of agglutinins. *J. Immunol.* **47**:133-147, 1943.
73. Stokes, J., Jr., Maris, E. P., and Gellis, S. S. Use of concentrated normal human serum gamma globulin (human immune serum globulin) in prophylaxis and treatment of measles. *J. Clin. Investigation* **23**:531-540, 1944.
74. Ordman, C. W., Jennings, C. G., and Janeway, C. A. Use of concentrated normal human serum gamma globulin (human immune serum globulin) in prevention and attenuation of measles. *J. Clin. Investigation* **23**:541-549, 1944.
75. Gellis, S. S., Stokes, J., Jr., Brother, G. M., Hall, W. M., Gilmore, H. R., Beyer, E., and Morrisey, R. A. Use of human immune serum globulin (gamma globulin) in infectious (epidemic) hepatitis in Mediterranean Theater of Operations. I. Studies on prophylaxis in two epidemics of infectious hepatitis. *J. A. M. A.* **128**:1062, 1945.
76. Havens, W. P., Jr., and Paul, J. R. Prevention of infectious hepatitis with gamma globulin. *J. A. M. A.* **129**:270-272, 1945.
77. Gellis, S. S., McGuinness, A. C., and Peters, M. Study on prevention of mumps orchitis by gamma globulin. *Am. J. M. Sc.* **210**: 661-664, 1945.

78. Ham, T. H., and Curtis, F. C. Plasma fibrinogen response in man: influence of nutritional state, induced hyperpyrexia, infectious disease and liver damage. *Medicine* **17**:413-445, 1938.
79. Morrison, I. R. Qualitative changes in fibrinogen which influence erythrocyte sedimentation rate and clot retraction time. *Am. J. M. Sc.* **211**:325-331, 1946.
80. Peters, J. P. Serum proteins in health and disease. *J. Mt. Sinai Hosp.* **9**:127-141, 1942.
81. Sabin, F. R. Cellular reactions to dye-protein with concept of the mechanism of antibody formation. *J. Exper. Med.* **70**:67-82, 1939.
82. Brand, E., Kassel, B., and Saidel, L. J. Amino acid composition of plasma proteins. *J. Clin. Investigation* **23**:437-444, 1944.
83. Bruckman, F. S., D'Esopo, L. M., and Peters, J. P. Plasma proteins in relation to blood hydration. IV. Malnutrition and serum proteins. *J. Clin. Investigation* **8**:577-590, 1930.
84. Hopper, J., Jr., Winkler, A. W., and Elkington, J. R. Simultaneous measurements of blood volume in man and dog by means of Evans blue dye, T-1824, and by means of carbon monoxide. II. Under abnormal conditions, including secondary shock. *J. Clin. Investigation* **23**:636-648, 1944.
85. Metcoff, J., Favour, C. B., and Stare, F. J. Plasma protein and hemoglobin in protein-deficient rat: three-dimensional study. *J. Clin. Investigation* **24**:82-91, 1945.
86. Lyons, R. C., Jacobson, S. D., and Neerkin, J. L. Relationship between changes in serum protein concentration and plasma volume in normal subjects. *J. Lab. & Clin. Med.* **30**:404-411, 1945.
87. Gregersen, M. I., Gibson, J. G., 2d, and Stead, E. A. Plasma volume determination with dyes: errors in colorimetry; use of blue dye T-1824. *Am. J. Physiol.* **113**:54, 1935.
88. Gibson, J. G., 2d, and Evans, W. A., Jr. Clinical studies of blood volume. I. Clinical application of method employing azo dye "Evans blue" and spectrophotometer. *J. Clin. Investigation* **16**: 301-316, 1937.
89. Gregersen, M. I. Practical method for determination of blood volume with dye T-1824: survey of present basis of dye-method and its clinical applications. *J. Lab. & Clin. Med.* **29**:1266-1286, 1944.
90. Noble, R. P., and Gregersen, M. I. Blood volume in clinical shock. I. Mixing time and disappearance rate of T-1824 in normal subjects and in patients in shock: determination of plasma volume in man from 10-minute sample. *J. Clin. Investigation* **25**:158-171, 1946.
91. Philips, R. A., Yeomans, A., Dole, V. P., Farr, L. E., and Van Slyke, D. D. Estimation of blood volume from change in blood specific gravity following plasma infusion. *J. Clin. Investigation* **25**: 261-269, 1946.
92. Gibson, J. G., 2d, and Evans, W. A., Jr. Clinical studies of blood volume. III. Changes in blood volume, venous pressure and blood velocity rate in chronic congestive heart failure. *J. Clin. Investigation* **16**:851-858, 1937.
93. Meneely, G. R., and Kaltreider, N. L. Study of volume of blood in congestive heart failure. Relation to other measurements in 15 patients. *J. Clin. Investigation* **22**:521-530, 1943.
94. Merrill, A. J. Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as primary cause of edema. *J. Clin. Investigation* **25**:389-400, 1946.
95. Perera, G. A. Increased plasma volume in cardiac insufficiency: its correlation with right-sided failure. *J. Clin. Investigation* **24**: 708-711, 1945.
96. Harris, A. W., and Gibson, J. G., 2d. Clinical studies of blood volume. VII. Changes in blood volume in Bright's disease with or without edema, renal insufficiency, or congestive heart failure, and in hypertension. *J. Clin. Investigation* **28**:527-536, 1939.
97. Peters, J. P. Water exchange. *Physiol. Rev.* **24**:491-531, 1944.
98. Thorn, G. W., Nelson, K. R., and Thorn, D. W. Study of mechanism of edema associated with menstruation. *Endocrinology* **22**:155-163, 1938.
99. Clinton, M., Jr., and Thorn, G. W. Effect of desoxycorticosterone acetate administration on plasma volume and electrolyte balance of normal human subjects. *Bull. Johns Hopkins Hosp.* **72**:255-264, 1943.
100. Soule, H. C., Buckman, T. E., and Darrow, D. C. Blood volume in fever. *J. Clin. Investigation* **5**:229-242, 1928.
101. Rutstein, D. D., Thompson, K. J., Tolmach, D. M., Walter, W. W., and Floody, R. J. Plasma volume and "extravascular thiocyanate space" in pneumococcus pneumonia. *J. Clin. Investigation* **24**: 11-20, 1945.
102. Gibson, J. G., 2d, and Harris, A. W. Clinical studies of blood volume. V. Hyperthyroidism and myxedema. *J. Clin. Investigation* **18**: 59-65, 1939.
103. Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry.* Volume I. 1264 pp. Baltimore: Williams & Wilkins Company, 1931.
104. Gibson, J. G., 2d, Harris, A. W., and Swigert, V. W. Clinical studies of blood volume. VIII. Macrocytic and hypochromic anemias due to chronic blood loss, hemolysis and miscellaneous causes, and polycythemia vera. *J. Clin Investigation* **18**:621-632, 1939.
105. Gibson, J. G., 2d. Clinical studies of blood volume. VI. Changes in blood volume in pernicious anemia in relation to hematopoietic response to intramuscular liver extract therapy. *J. Clin. Investigation* **18**:401-414, 1939.
106. Feldman, H. A., and Murphy, F. D. Effect of alterations in blood volume on anemia and hypoproteinemia of human malaria. *J. Clin. Investigation* **24**:780-792, 1945.
107. Thomson, K. J., Hirsheimer, A., Gibson, J. G., II, and Evans, W. A., Jr. Studies on circulation in pregnancy. III. Blood volume changes in normal pregnant women. *Am. J. Obst. & Gynec.* **36**: 48-59, 1938.
108. Swingle, W. W., Parkins, W. M., Taylor, A. R., and Hays, H. W. Study of water intoxication in intact and adrenalectomized dog and influence of adrenal cortical hormone upon fluid and electrolyte distribution. *Am. J. Physiol.* **119**:557-566, 1937.
109. Thorn, G. W., Howard, R. R., and Emerson, K., Jr. Treatment of Addison's disease with desoxy-corticosterone acetate, synthetic adrenal cortical hormone (preliminary report). *J. Clin. Investigation* **18**:449-467, 1939.
110. Jacobson, S. D., and Lyons, R. H. Changes in blood volume produced by diabetic acidosis. *J. Lab. & Clin. Med.* **27**:1169-1173, 1942.
111. Darrow, D. C., and Yannet, H. Metabolic studies of changes in body electrolyte and distribution of body water induced experimentally by deficit of extracellular electrolyte. *J. Clin. Investigation* **15**:419-427, 1936.
112. Winkler, A. W., Danowski, T. S., Elkington, J. R., and Peters, J. P. Electrolyte and fluid studies during water deprivation and starvation in human subjects, and effect of ingestion of fish, of carbohydrate, and of salt solutions. *J. Clin. Investigation* **23**:807-815, 1944.
113. Gibson, J. G., 2d, and Kopp, I. Studies in physiology of artificial fever. I. Changes in blood volume and water balance. *J. Clin. Investigation* **17**:219-232, 1938.
114. Ebert, R. V., Stead, E. A., Jr., and Gibson, J. G., II. Response of normal subjects to acute blood loss, with special reference to mechanism of restoration of blood volume. *Arch. Int. Med.* **68**: 578-590, 1941.
115. Richards, D. W., Jr. Circulation in traumatic shock in man. Harvey Lecture. *Bull. New York Acad. Med.* **20**:363-393, 1944.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 33011

PRESENTATION OF CASE

A thirty-five-year-old operator of a mink farm and dog kennel entered the hospital because of difficulty in swallowing.

Eight days before entry the patient, as well as the other members of his family, had had a mild bout of diarrhea, which had subsided completely in two days. Four days before entry he noticed a slight pain in the back and on the next day developed nausea and vomiting. In the evening the temperature rose to 100.5°F. Vomiting continued; the palate became sore and swollen, and the temperature rose to 102°F. On the day of admission the nausea abated, but difficulty in swallowing developed, so that mucus and saliva collected in the throat, causing great discomfort and difficulty in breathing. The patient gagged on liquids unless he was extremely careful. He regurgitated fluids through his nose and could not open his mouth as wide as usual. He had had no headaches, diplopia, pain, muscle tenderness or cough.

During the previous winter many of the patient's dogs had died from a virus infection identified at a state university as similar to but not identical with distemper.

Physical examination revealed a well nourished man whose respirations were shallow but not rapid. He was not cyanotic. The voice was thick and indistinct and had a nasal quality. The pharynx was injected. There was a Grade II, blowing systolic murmur heard best over the sternum slightly to the left of the midline in the third interspace. The lungs and abdomen were normal. Neurologic examination showed a questionable weakness of the left side of the face. The pharyngeal constrictors were weak. The neck muscles — particularly the right sternomastoid — were weak. The neck was not stiff. The arms and legs had good strength. There was no muscle tenderness. The tendon reflexes in the arms were not obtainable. The right knee jerk was questionably absent; the left knee jerk and both ankle jerks were present. There was an extensor plantar reflex on the right. Sensation was normal.

The temperature was 104.3°F., the pulse 80, and the respirations 28. The blood pressure was 140 systolic, 60 diastolic.

Examination of the blood disclosed a hemoglobin of 16 gm. and a white-cell count of 12,000, with 72 per cent neutrophils. The urine was normal. The spinal fluid had an initial pressure equivalent to 200 mm. of water. There were 26 lymphocytes and 2 polymorphonuclear leukocytes per cubic millimeter. The total protein was 70 mg., the sugar 86 mg. and the chloride 667 mg. per 100 cc. The gold-sol test was 0001232110.

Despite frequent suctioning of the pharynx the patient was unable to sleep because of the accumulating mucus. The respirations were good. On the second hospital day, the temperature dropped to 100°F., and he appeared somewhat improved. Nevertheless he was started on prophylactic penicillin at the rate of 24,000 units every three hours. During the night, he again had difficulty with mucus. On the third hospital day he was disoriented and picking at the bedclothes. Breathing was good, and the chest clear. The temperature rose to 101°F.

On the fourth hospital day the patient was unresponsive, cyanotic and bathed in perspiration. The lungs were clear, and the chest expanded well without the use of accessory muscles. The temperature now fell to 98°F. After the administration of oxygen by mask the cyanosis diminished and the pulse rate improved. The patient was then placed in a respirator. Breathing was gasping, irregular and asynchronous with the respirator. Mucus gathered rapidly. The pulse gradually became too weak to be felt. Finally, respirations ceased.

DIFFERENTIAL DIAGNOSIS

DR. JAMES B. AYER: We are evidently dealing with a rapidly progressive, acute, febrile disturbance affecting chiefly the brain stem, particularly the medulla. That a lesion or lesions were present in the medulla is indicated by the abnormal findings in the spinal fluid, which suggest either a virus infection or a reaction to local irritation. Although the lesion was dominant in the medulla and pons and undoubtedly caused the patient's death, there is some evidence that the spinal cord was also involved, as shown by the absent reflexes in the arms and the unequal reflexes in the legs. The terminal disorientation does not necessarily indicate implication of the cortex, the mental picture being readily explained on the basis of anoxemia.

In so-called "acute bulbar palsy" many diagnoses must be considered. All forms of acute bacterial meningitis are excluded by the absence of meningeal symptoms and by the type of spinal fluid.

Diphtheria is a possibility, but the lack of mention of a membrane in the throat and the abnormal spinal-fluid findings exclude this diagnosis.

We are constantly reminded that the patient was associated with animals, both sick and well. This suggests tularemia and brucellosis, which in this vicinity are more chronic in their course, without pronounced affection of the nervous system. Rabies runs a course even shorter than that in this case. The chief symptom — hydrophobia — is not mentioned, and the spinal fluid in such cases is normal. As for distemper, it is my understanding that this disease does not attack man.

Food poisoning, suggested by the fact that the patient and his family had mild attacks of diarrhea, indicates the possibility of botulism and other neurotropic poisons. It is my impression that none of these give abnormal spinal-fluid findings; nor is the gastrointestinal picture a dominant one. Myasthenia gravis may cause death from respiratory paralysis, as may infectious polyneuritis. But the clinical picture and course are so different from those in the case under discussion that they can hardly be considered.

A frequent cause of acute bulbar palsy is thrombosis of the basilar artery or its branches. In a patient of this age the usual etiologic factor, arteriosclerosis, should be absent. The presence of a septic embolus may be considered because of the cardiac murmur, but it is usual for emboli to pass up the internal carotid arteries rather than the vertebral vessels.

By process of exclusion, none of the above diagnoses fit this case. The onset, the clinical course, the symptomatology and the physical and spinal-fluid findings are typical of acute poliomyelitis of the bulbar type, which is my diagnosis. Incidentally, if this case had been reported twenty-five years ago, I should have included encephalitis lethargica as of equal likelihood to poliomyelitis — the findings in the bulbar types of that disease were in every way consistent with those in this patient. My diagnosis of acute poliomyelitis of the bulbar type is made with the reservation that my knowledge of animal diseases causing virus infections of the nervous system is limited.

Dr. Augustus S. Rose: I should like to ask Dr. Ayer to discuss the recurrence of the Babinski sign.

Dr. Ayer: It sometimes happens in poliomyelitis that, although the gray matter is primarily involved, the white matter is also infiltrated and a transitory, not a permanent, Babinski sign is found. That was characteristic of the cases of encephalitis lethargica that simulated poliomyelitis. Also, one wonders if the Babinski sign was persistent; a single observation of a positive sign must be confirmed.

Dr. Rose: I should also like to ask about the absence of a stiff neck in bulbar poliomyelitis.

Dr. Ayer: That is not so frequent in this type as in poliomyelitis affecting the spinal cord.

There are two additional points that should be mentioned. In an epidemic in this vicinity some years ago, Crone* analyzed a series of cases of bulbar poliomyelitis in which the reaction of the patients in the respirator was of great interest. They died not only in spite of the respirator but also, perhaps, because of it. It is interesting that in this case the intercostal muscles were spared.

The second point is that in these cases the higher the sugar in the spinal fluid, the worse the prognosis; that has never been explained to my knowledge. The sugar was elevated in this case. The temperature was high for the usual case of poliomyelitis. Why did you not ask about that? Patients with bulbar poliomyelitis often run high temperatures, whereas those with the ordinary type run temperatures of around 100 to 102°F. — usually 101°F.

Dr. Charles S. Kubik: You saw the patient, Dr. Rose. Do you wish to add anything?

Dr. Rose: We thought that this was a case of bulbar poliomyelitis. We considered the extensor plantar reflex on the one hand and the difficulty in the respirator on the other to have been due to bulbar involvement outside the anterior-horn cells — in other words, that encephalitis, as well as anterior poliomyelitis, was present.

Dr. Ayer: The diagnosis may well include encephalitis, but the terminal picture was hardly enough to indicate encephalitis because anoxemia offers a sufficient explanation.

Clinical Diagnosis

Anterior poliomyelitis, bulbar type.

Dr. Ayer's Diagnosis

Acute poliomyelitis, bulbar type.

Anatomical Diagnosis

Poliomyelitis, bulbar type.

Pathological Discussion

Dr. Kubik: This was a case of poliomyelitis. The temperature, which was high on admission, dropped and rose again. Because of the difficulty in swallowing, the question of aspiration pneumonia was raised. There was bronchopneumonia, but no definite aspiration pneumonia. As in most fatal cases of poliomyelitis there were lesions not only in the medulla and spinal cord but also in the pons, midbrain, basal ganglions and cerebral cortex.

The cortical lesions are usually not extensive, and so far as I know never give rise to focal signs; in my experience they are likely to be found in the anterior central convolutions. Another interesting feature is that there is usually good functional recovery of the paralyzed bulbar muscles in nonfatal cases of poliomyelitis and that there is, as a rule, comparatively little destruction of the nerve cells

*Crone, N. L. Treatment of acute poliomyelitis with respirator. *New Eng. J. Med.* 210:621-623, 1934.

in the motor nuclei of the brain stem, even in severe and fatal cases with extensive microglial proliferation and perivascular infiltration in the same nuclei.

The anterior-horn cells of the spinal cord, for some reason, are particularly vulnerable. In another case all the anterior-horn cells on both sides were destroyed, whereas the cells of the columns of Clarke were intact. In the same case, in which death occurred five weeks after the onset, the cells had degenerated in a posterior root, presumably indicating degeneration of cells of a posterior spinal ganglion. Involvement of the ganglions or of the ganglions and posterior roots, probably explains the radicular type of pain that is often present in the early stages of the disease.

CASE 33012

Presentation of Case

A forty-seven-year-old credit manager was admitted to the hospital with a history of cough.

Four months before admission, the patient had caught a "cold," following which a cough had persisted intermittently. He raised moderate amounts of foamy sputum with occasional flecks of bright-red blood. There were four febrile episodes, each lasting for about a week, during which the cough and sputum were accentuated. In the afternoons the temperature rose to 101 and occasionally to 103°F., with chilly sensations but no shaking chills. During this period the patient lost 15 pounds in weight. There had been a feeling of soreness and occasionally of pain in the left upper anterior portion of the chest that in the last three days before admission had become pleuritic. At the onset of the cough x-ray examination had revealed what was called a "tumor" in the left upper portion of the lung, and bronchoscopy had disclosed only inflammation, according to the patient. A month before admission another x-ray film revealed the same findings, and arrangements were made for admission to the hospital. For the next three weeks he complained of hoarseness and anorexia.

The patient had had poliomyelitis as an infant, with paralysis of the right leg and left foot and subsequent recovery except for considerable atrophy and some shortening of the right leg. He had had the usual childhood diseases, as well as typhoid fever at the age of ten. About ten years before entry, he complained of right midabdominal pain, and four years later a "hypernephroma" of the right kidney was removed. An x-ray examination of the lungs was made every three months until four years before admission, with negative findings, and the patient remained completely healthy until the onset of the present illness, except for occasional attacks of mild diarrhea.

Physical examination revealed a well developed and well nourished man. The trachea was slightly deviated to the left. There were some dullness to percussion over the left upper portion of the chest and marked diminution of breath sounds and tactile and vocal fremitus over the left upper anterior and posterior portions of the chest and apex. There appeared to be slightly less expansion of the chest on the left upper side than on the right. The voice was hoarse, and there were occasional red macules, 1 to 4 mm. in diameter, on the chest. The right leg was about 2.5 cm. shorter than the left. There was atrophy of the muscles of the right leg and of the left calf. There was a definite scoliosis of the spine to the right.

The temperature was 98.8°F., the pulse 92, and the blood pressure 130 systolic, 90 diastolic.

Examination of the blood disclosed a hemoglobin of 11.2 gm. and a white-cell count of 23,200, with 82 per cent neutrophils; the red cells were moderately hypochromic. The urine had a specific gravity of 1.022 and gave a ++ test for albumin, with rare granular casts, 25 red cells and 2 white cells per high-power field in the sediment. The nonprotein nitrogen was 27 mg., and the total protein 7.7 gm. per 100 cc.

X-ray examination revealed an extensive hazy density occupying the lower anterior portion of the left upper lobe; the interlobar septum was displaced forward. There was also a lobulated area of density extending upward into the midportion of the upper lobe. On the right side, there were areas of calcification in the hilus and there was hazy density in the first interspace, more marked toward the axillary line. The dorsal spine showed curvature to the right, but the bones were otherwise not remarkable. A process in the right infraclavicular region had developed since previous films taken elsewhere. There was marked curvature of the upper lumbar spine, with convexity to the left and a spur formation of the right lateral margins of the vertebral bodies in this region. The skull, dorsolumbar spine and pelvis showed no evidence of metastases.

The patient developed a daily evening elevation of temperature to 102°F., with occasional pleuritic pains in the left upper portion of the chest anteriorly and a cough productive of thin, watery, mucoid sputum without blood. The chest signs remained unchanged. Penicillin had little effect on the fever. On the eighth day an operation was performed.

Differential Diagnosis

Dr. Joseph C. Aub: The past history suggests two diagnoses — primary tumor of the lung and metastasis from a so-called "hypernephroma" (renal-cell adenocarcinoma). Whatever the lesion was, it could have involved the recurrent laryngeal nerve. The patient had had symptoms for four years before the hypernephroma was removed. That is a long

time. I do not know what the red macules on the chest were. They may have been important.

DR. TRACY B. MALLORY: The dermatologist's opinion was that they were characteristic of bromide rash.

DR. AUB: The scoliosis immediately makes one doubt the significance of any physical findings in the chest, because as soon as severe scoliosis is encountered, physical findings in the chest are altered by changes in aeration in the lung. The increased white-cell count and the red cells in the urine could have been due to hypernephroma involving the vena cava and obstructing the return blood flow from the other kidney, or to metastases to the other kidney.

The course suggests metastases not from the lung but from elsewhere, and one thinks, of course, of hypernephroma. The elevated temperature might have been due to either a primary infection or one caused by an occluding neoplasm. It does not establish an infection, however, because hypernephroma in itself causes fever. The pleuritic pain is also somewhat more suggestive of hypernephroma than of primary tumor of the lung, unless there was a good deal of infection, with subsequent irritation of the pleura, due to the primary tumor of the lung.

The patient was operated on on the eighth day. The type of procedure performed must be questioned. This was not the type of case that requires an extensive operation. If this man had been my patient, I should have handled him by doing a bronchoscopy, which is probably the operation that is referred to.

In these discussions I do not like to put in every possible diagnosis so as to be sure to include everything that was wrong with the patient. I think that it is better to list only likely diagnoses. There are three probable diagnoses in this case. One is primary infection of the lung that lasted four months and came and went, giving the recurrent symptoms, but that seems unlikely. Although the first bronchoscopy showed only chronic infection, a primary bronchiogenic neoplasm and metastases of a hypernephroma are the other two conditions that need serious thought. The diagnosis practically depends on the x-ray films. I do not believe that a proper differential diagnosis can be made without inspection of the films, but before that I should like to make one or two remarks. I think that this was probably a neoplasm; the most important thing is the location. If it was close to the hilar region, one must make the diagnosis of a primary, bronchiogenic neoplasm, with infection behind it caused by obstruction of the bronchus. If the neoplasm was out in the periphery it was probably metastatic hypernephroma. A duration of six years is not too long for metastases from a hypernephroma. I have seen cases in which these tumors were silent for thirteen years and then ran a virulent course, in spite of the fact that hypernephroma generally metastasizes early.

May we see the x-ray films?

DR. LAURENCE L. ROBBINS: We have the good fortune of having the original films that were taken at the onset of the illness. They show the beginning of the lesion in the left upper lobe. Films taken while the patient was in the hospital show a considerable increase in the process. It first started as a rather nodular lesion, suggesting a multiplicity of nodules. By the time of admission there had been involvement of the lingular and lateral branches of the left upper lobe. There was some collapse, and the process was located in the anterior portion of the upper lobe. So far as could be determined at the original examination, the right upper-lung field was clear, and on the second examination it was essentially so; by the time the patient entered the hospital, however, there was evidence of something abnormal in the right upper lobe. I put up this film of the abdomen because it shows the scoliosis that was noted. There is a shadow in the region of the right kidney, which is not unusual, since after the kidney has been removed a shadow is frequently seen, suggesting that the kidney is still there — apparently, the area fills in with blood and the perirenal fat persists. I do not see the shadow of the psoas muscle, possibly because of the scoliosis.

DR. DONALD S. KING: The dates of these films are interesting.

DR. ROBBINS: This first film was taken in April, 1945, and the next series in March, 1946.

DR. AUB: The indefinite lesion in the right apex was probably important, but I shall neglect it because I do not know what it is. The danger in not making a diagnosis of hypernephroma is that such a tumor often metastasizes to the lung; one should not make the mistake of neglecting it, saying that the lesion in the lung is a new one. It is probably unwise to do so, but I am going to do just that. The reason I do not believe that this was hypernephroma is that the position of the lesion was unusual for that diagnosis. The facts that sway me are that it was a single lesion, that it had been present for a year, that it started fairly near the hilus and extended along lines that look like the bronchi, and that the lung had collapsed peripheral to the tumor, suggesting that the lesion had occluded a bronchus rather than being out in the alveoli originally. I think that this man had infection in the collapsed upper lobe beyond the occluded bronchi. I have not forgotten, as I pointed out above, that patients with hypernephroma are likely to have fever without apparent infection. I think that this man had a primary bronchiogenic neoplasm, which may well not have been found at bronchoscopy because it was in a location difficult to see. As a matter of fact, I should not be surprised to hear that this had been caused by a metastasis from the hypernephroma — indeed, I consider it highly likely that it was. That is my second guess.

DR. KING: I should like to ask Dr. Castleman whether it is true that a hypernephroma often metastasizes to the lumen of the bronchus.

DR. BENJAMIN CASTLEMAN: It metastasizes somewhat in the manner of a sarcoma. It may metastasize to the bronchus and may produce spitting of blood. Dr. King and I looked up this point some years ago.

DR. MALLORY: We have made a diagnosis of hypernephroma on bronchoscopic biopsy in at least one case — possibly more.

What procedure was performed, Dr. King?

DR. KING: A lobectomy. We did not do another bronchoscopy. The patient had been bronchoscoped outside the hospital, and nothing had been found. Operation seemed indicated in any event.

CLINICAL DIAGNOSIS

Metastatic hypernephroma of left upper lobe of lung.

DR. AUB'S DIAGNOSIS

Primary bronchiogenic neoplasm, with collapse of lung alveoli and local infection.

ANATOMICAL DIAGNOSIS

Metastatic renal-cell adenocarcinoma (hypernephroma) of left upper lobe of lung.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The specimen was an interesting one. We did find a metastatic renal-cell adenocarcinoma (hypernephroma). Almost the entire tumor lay within the bronchial tree, predominantly in the branches running toward the upper portion of the lobe. They appeared to be completely obstructed by plugs of tumor tissue, but the obstruction could not have been complete because the pulmonary tissue beyond the obstruction was not collapsed but was emphysematous. The alveoli were uniformly dilated, as they are in bronchial asthma or other conditions in which there is incomplete obstruction of the bronchus. There was an area of chronic pneumonitis of considerable size near the base of the lobe, but the bronchi leading to that area were not obstructed, so that although Dr. Aub's logic is excellent, the specimen does not bear it out in any way.

DR. AUB: I should have discussed that because the x-ray films showed the neoplasm in areas where there was perfectly good aeration and did not indicate neoplasm in the areas where there was collapse.

DR. KING: We should probably have operated even if we had known it was hypernephroma, in the hope that we could rid the patient of metastases. There is the famous case of the patient who is living twelve years after the removal of such a pulmonary metastasis by Dr. Churchill.[1,2] That is one reason why we went ahead and tried to find x-ray evidence of metastases before operation — we could not find it.

Three weeks after operation the patient came in to the office with severe pain in the neck requiring morphine. In addition, he had a soft-tissue mass on the top of the head; x-ray examination showed a bony defect in the skull. He returned to the hospital, and gradually the pain went away. Later the mass on the top of the head disappeared. He had one convulsion and paralysis of the right leg; the paralysis also cleared. At present, several months after operation, the patient is better than he has been for a long time. I do not know what became of the soft-tissue mass in the scalp.

DR. MALLORY: Had any x-ray treatment been given, Dr. Robbins?

DR. ROBBINS: Not so far as I know.

DR. KING: The patient was not given any; he had received some stilbestrol but only for a few days. It upset his stomach and was consequently discontinued.

DR. ROBBINS: This is the film taken prior to operation. I do not know whether you can see the definite defect in this portion of the parietal bone — it has disappeared since the original film. There was an area of approximately 2 cm. in length involving the outer table. The inner table is well preserved.

DR. ALLEN G. BRAILEY: What was the cause of the signs in the right apex?

DR. KING: More metastases, but we have not taken an x-ray film since then.

DR. MALLORY: The patient was placed on penicillin six days before operation, with quite a marked effect on the temperature chart. The day after operation the temperature dropped to normal. We still do not know whether the fever was due to pneumonitis or to the hypernephroma.

DR. AUB: Does hypernephroma cause fever without any other obvious cause?

DR. MALLORY: Unquestionably.

DR. AUB: This is another example of the fact that one should always pick out the obvious diagnosis.

REFERENCES

1. Barney, J. D., and Churchill, E. D. Adenocarcinoma of kidney with metastasis to lung cured by nephrectomy and lobectomy. *Tr. A. A. Genito-Urin. Surgeons* 31:71-79, 1938.
2. Barney, J. D. Twelve-year cure following nephrectomy for adenocarcinoma and lobectomy for solitary metastasis. *J. Urol.* 406, 1944.

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FURTHER REASONS FOR THE NURSE SHORTAGE

A letter appearing elsewhere in this issue of the *Journal* was prompted by an editorial, "Shortage of Nurses," that was carried in the issue of September 12. The correspondent emphasizes that the life of the nurse in training is far from ideal, particularly as it pertains to recreational and social activities. Although it has long been an accepted idea that a nurse in training should lead a life in many respects comparable to that of a nun, there is little doubt that there is no need for such an attitude to persist in this present day and generation. That his statements in this regard are generally true is open to question; on the other hand, all training schools should make a careful study to determine whether any change in the regulations governing the social life of their students is indicated.

The remarks concerning the traditional attitude of the surgeon in the operating room also call for careful and thoughtful consideration. Picturesque as the old-time martinet master surgeon may have been, and interesting and amusing as it may be to read of the nurses and interns as they stood cowering about the operating table of the master and unable to make any defense against his attack, it is true that all these fireworks accomplished less than nothing regarding the care these subordinates gave in the particular case on the operating table. Nor did they prevent the reoccurrence of mistakes. It is surprising to observe the quick and eager response and the gratitude that result from a few quiet words of advice and a brief explanation of what the surgeon wants; furthermore, such conduct is extremely effective in attaining the desired result in the future. With service in the armed forces so recent to many, it is worth while recalling that one rule of the Army is excellent, even though it was not by any means universally applied: "Superiors are forbidden to injure those under their authority by tyrannical or capricious conduct or by abusive language."* This regulation recognizes the absolute necessity of treating subordinates in such a manner that their self-respect is preserved, and this attitude is equally applicable to civilian life.

There appears to be no single reason for the present shortage of nurses. It would be helpful, however, if hospitals, training schools and their professional staffs would do their part in making the life of a nurse more attractive than it is at present, thereby encouraging more young women of the proper type to enter the nursing profession.

*Paragraph 3, Army Regulations 600-100.

DOCTORS EAST, DOCTORS WEST

Dr. Edward H. Hume,* under the title *Doctors East, Doctors West*, has recently published the account of his establishment of the Yale Hospital in Changsha in 1906, and the later founding of the Yale-in-China school of medicine. It is a book of intense interest to any doctor concerned with the

*Hume, E. H. *Doctors East, Doctors West*. 278 pp. New York: W. W. Norton and Company, Incorporated, 1946.

extension of his art and science, and to the student of Chinese ways and culture and history.

It was only two years after the treaty opening Hunan Province to foreigners, and only five years after the memorable Boxer Rebellion, that Dr. Hume entered what had been virtually a forbidden city; a year later he opened the Yali Hospital, and waited for Yale's first patients in China. The story of the hospital's early days in the community and the place that it eventually found for itself, the starting of the medical school, the erection of new buildings, the Harkness gift and the eventual turning over of the Hsiangya Medical Educational Association to the provincial government make fascinating reading.

The substance of the book, however, is in the title, for its real story is of the meeting of Occidental with Oriental medical culture, and the lessons that each had to learn. According to a Chinese proverb,

To read the medical classics exhaustively
Is not equal to frequent visits to the sick,

and as some evidence of the value of this advice we find published about the year 196 A.D. a treatise on typhoid fever by Chang Chungching, giving an accurate clinical description of the disease, with the advice to avoid violent purgatives in its treatment and to reduce the fever with cooling baths. Seaweed extracts for the treatment of certain kinds of goiter are recommended in classic Chinese medical literature, and fish-liver oils for tuberculosis; inoculation against smallpox was practiced from early times. One of the most interesting examples of Chinese medical perspicuity is found in the story of a Western woman treated unsuccessfully for pernicious anemia by Sir Patrick Manson in Amoy. Later a Chinese physician of the old school offered to cure her — and did — with large doses of crow's liver, decades before modern medical science had discovered the liver treatment of the disease!

Dr. Hume tells of his consultation with Dr. Wang, of the old school, and of their mutual arrival at the same diagnosis by different methods, for

By nature men are nearly alike;
Their customs differ widely,

and of his invitation to Dr. Wang to give a course of lectures on the old art at the new medical school. This was, indeed, the attitude that particularly fitted the author for his post, for

He who looks back to the old
And knows the new
Is worthy to be a scholar.

MASSACHUSETTS MEDICAL SOCIETY

BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

DEATHS

BERGERON — George G. Bergeron, M.D., of Ludlow, died September 26. He was in his fifty-sixth year.

Dr. Bergeron received his degree from Temple University School of Medicine in 1917. He was a fellow of the American Medical Association.

SIMMONDS — Frederick J. Simmonds, M.D., of Jamaica Plain, died December 6. He was in his sixty-ninth year.

Dr. Simmonds received his degree from Middlesex University School of Medicine in 1917. He was a fellow of the American Medical Association.

His widow survives.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PRIORITY SYSTEM ON FREE WHOLE BLOOD

When needed, whole blood may be obtained free by actual donors and members of their immediate families under a priority system now in effect for the Massachusetts Blood Donor Program. (Doctors and hospitals may continue to charge their usual fee for administration.)

Originally it was believed that the program could not undertake the distribution of whole blood until some time in 1947. The return of Army-Navy surplus stocks of plasma, however, enabled the Department of Public Health to supply Massachusetts hospitals with plasma from this reserve instead of using the blood from current donations for plasma production. This made it possible for the Department to turn its attention to processing fractions and developing the whole-blood phase of the program. In September, 1946, the Blood Donor Program began to furnish free whole blood for people who had actually donated to the program and for members of their immediate families. Although the distribution of whole blood has increased, there is still not enough to meet the need throughout the Commonwealth. The program is expanding steadily, however, and efforts are being made to extend the

program to include every Massachusetts resident as soon as possible.

In order to ensure a fair distribution of the whole blood that is currently available, the following priority system has been set up: *first priority* includes actual donors and members of their immediate families; *second priority* is given to residents of communities in which the Mobile Unit has taken blood; *third priority* goes to residents of communities in which the Mobile Unit is definitely scheduled to visit; and *fourth priority* takes in all other residents of Massachusetts. Emergency cases are given first consideration anytime that the required type of blood is on hand.

SCHEDULE FOR MOBILE-UNIT VISITS

The Mobile Unit of the Massachusetts Blood Donor Program will make the following visits in the near future.

PLACE	DATE
New Bedford	January 27, 28 and 29
Stoneham	January 31

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR NOVEMBER, 1946

Résumé

DISEASES	NOVEMBER 1946	NOVEMBER 1945	SEVEN-YEAR MEDIAN
Anterior poliomyelitis	55	46	10
Chancroid	2	1	*
Chicken pox	770	771	1025
Diphtheria	61	17	17
Dog bite	664	631	592
Dysentery, bacillary	3	9	24
German measles	63	55	55
Gonorrhea	378	509	426
Granuloma inguinale	0	0	*
Lymphogranuloma venereum	0	1	*
Malaria	15	44	2
Measles	691	657	816
Meningitis, meningococcal	6	7	12
Meningitis, Pfeiffer-bacillus	5	5	3
Meningitis, pneumococcal	1	5	4†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	0	1	0†
Meningitis, other forms	1	0	1†
Meningitis, undetermined	1	3	5†
Mumps	306	523	523
Pneumonia, lobar	61	92	225
Salmonella infections	14	7	5
Scarlet fever	294	466	704
Syphilis	303	391	419
Tuberculosis, pulmonary	227	241	215
Tuberculosis, other forms	12	9	16
Typhoid fever	3	3	2
Undulant fever	5	4	4
Whooping cough	598	661	661

*Made reportable December, 1943.
†Four-year average.

Comment

Diseases reported at an incidence above the seven-year median included anterior poliomyelitis, diphtheria, German measles, malaria, Salmonella infections, typhoid fever and tuberculosis.

Diseases reported at an incidence below the seven-year median included chicken pox, bacillary dysentery, measles, meningococcal meningitis, mumps, lobar pneumonia, scarlet fever and whooping cough.

Diphtheria was reported at the highest prevalence for this month since 1933, being three times that of the corresponding month of last year.

Poliomyelitis continued to occur much later than usual, resulting in a higher number of cases for the month than in 1945, although the total cases for the year to date is much lower.

Lobar pneumonia continued to manifest the lowest incidence for this month, being less than one fourth that of the seven-year median. It again shattered the all-time record.

Geographical Distribution of Certain Diseases

Anterior poliomyelitis was reported from: Arlington, 1; Ashburnham, 8; Athol, 1; Boston, 5; Brookline, 2; Dover, 1; Easthampton, 3; East Bridgewater, 1; East Longmeadow, 1; Everett, 1; Falmouth, 1; Fall River, 1; Ipswich, 1; Lowell, 1; Lynn, 5; Milton, 1; Needham, 1; New Bedford, 1; Newton, 6; Orange, 1; Randolph, 1; Somerville, 1; Springfield, 1; Swampscott, 1; Upton, 1; Watertown, 1; Weston, 2; Worcester, 4; total, 55.

Diphtheria was reported from: Arlington, 1; Billerica, 1; Boston, 17; Brockton, 1; Cambridge, 2; Chelsea, 3; Dedham, 2; Easthampton, 1; Lowell, 3; Lynn, 1; Marlboro, 1; Medford, 2; New Bedford, 1; Newton, 1; Palmer, 1; Randolph, 3; Somerville, 14; Watertown, 2; Westboro, 2; Woburn, 1; Worcester, 1; total, 61.

Dysentery, amebic, was reported from: Murphy General Hospital, 1; total, 1.

Dysentery, bacillary, was reported from: Boston, 1; Worcester, 2; total, 3.

Encephalitis, infectious, was reported from: Haverhill, 1; North Adams, 1; total, 2.

Malaria was reported from: Amesbury, 1; Boston, 7; Leominster, 1; Montague, 1; Murphy General Hospital, 3; Springfield, 1; Worcester, 1; total, 15.

Meningitis, meningococcal, was reported from: Boston, 1; Lowell, 1; Montague, 1; New Bedford, 1; Worcester, 2; total, 6.

Meningitis, Pfeiffer-bacillus, was reported from: Billerica, 1; Cambridge, 1; Fall River, 1; Medway, 1; Salem, 1; total, 5.

Meningitis, pneumococcal, was reported from: Everett, 1; total, 1.

Meningitis, other forms, was reported from: Lowell, 1; total, 1.

Meningitis, undetermined, was reported from: Haverhill, 1; total, 1.

Salmonella infections were reported from: Boston, 1; Everett, 1; Haverhill, 4; Northfield, 2; Quincy, 1; Revere, 1; Salem, 3; Wellesley, 1; total, 14.

Septic sore throat was reported from: Amesbury, 8; Boston, 6; Merrimac, 7; Somerville, 1; total, 22.

Trichinosis was reported from: Bridgewater, 1; Malden, 1; Worcester, 2; total, 4.

Typhoid fever was reported from: Lowell, 1; Somerville, 1; Worcester, 1; total, 3.

Undulant fever was reported from: Gardner, 1; Northfield, 1; Quincy, 1; Southampton, 1; Worcester, 1; total, 5.

CORRESPONDENCE

SHORTAGE OF NURSES

To the Editor: Reading the editorial "Shortage of Nurses" in the September 12 issue of the *Journal* was stimulus sufficient to make for finding and reading the editorial in the July 11 issue of the *Journal* and the editorial "The Training of the Graduate Nurse" in the July issue of the *Virginia Medical Monthly*.

These articles take cognizance of the shortage of nurses, and in one it is suggested that the situation is a consequence of increasing educational requirements demanded for the registration of graduates. The seriousness of this state of affairs is apparent to all in the medical profession, and therefore needs no further comment.

The motive for this letter came from the conviction that one obvious source of information had been neglected, that is, the student nurse herself. Accordingly, I have, in the past few months, spoken to many nurses, attempting to unearth reasons why the profession is no longer so desirable as it once was.

The major criticism was directed at the training itself. Graduates frequently said that if they had the choice to make again they would certainly not go into nursing training. A paradox was pointed out in that only girls whose high-school records indicated superior ability were accepted by the training schools of the better hospitals. Yet the demands on the trainees in these hospitals precluded learning to a large degree. Learning, it was thought, stopped almost entirely after the first year, for thereafter the hospitals seemed so bent on exacting the worth of the food and lodging supplied the trainee in actual work mass that a state of chronic fatigue

supervened. This prohibited intelligent reading; attention at lectures vacillated. Regarding duties, a tendency toward automatism became increasingly great and interest waned in why a patient with a given disease received a particular kind of therapy. Initiative succumbed as the consciousness of not learning became engulfed in a despair at being able to learn.

The attitudes of physicians toward students were often thought to be not that of gentlemen. Cursing, harsh words, incessant satire all were mentioned, frequently with rancor. Few doctors ever troubled to explain what was being done or why it was being done — as in the operating room, where the student worked for weeks watching operations designed to accomplish she knew not what, on patients she knew nothing of.

The social restrictions of a trainee's life weighted heavily with every nurse consulted. It seemed not at all clear to them as trainees, why they should lead cloistered lives. They are allowed liberty until midnight on five nights each month, whereas girls of comparable age in colleges or in their homes are considered mature enough to decide how often and how long social activities should be indulged in. An incongruity is manifest when this attitude is referred to a nurse's responsibilities with a seriously ill patient.

Finally, it was pointed out that following graduation, a registered nurse could expect a job working for more than eight hours at various times during the twenty-four hours of the day. Exposure to all the ills of mankind would be her lot, and for this she would receive less money than many secretaries — special duty nurses, it was admitted, do fare well financially.

These thoughts were garnered in talking with nurses at the various hospitals to which students in the Harvard Medical School are assigned. I think that they certainly are valid and active reasons why there is a shortage of nurses. An examination of training-school statistics will reveal that some classes lose as many as 50 per cent of their original enrollment — admittedly, not all losses are due to the defects in the character of the training as described.

Succinctly, it is fair to say that from the point of view of the nurse, the shortage of nurses could in large measure be repaired by making the life of a student nurse more attractive — that is, by devoting more of the required three years to teaching and less of it to drudgery, by a real effort on the part of hospital staffs to improve attitude and conduct toward trainees, by attributing to student nurses a degree of maturity enjoyed by comparable groups of young women and by providing more nearly adequate recompense for graduates.

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BOOK REVIEW

A Bibliography of Infantile Paralysis, 1789-1944: With selected abstracts and annotations. Prepared under the direction of The National Foundation for Infantile Paralysis, Incorporated. Edited by Morris Fishbein, M.D. Compiled by Ludvig Hektoen, M.D. 4°, cloth, 672 pp. Philadelphia: J. B. Lippincott Company, 1946.

A bibliography of infantile paralysis has long been needed by the medical profession, librarians, public-health officials and the public at large. The subject has grown to vast proportions, and Dr. Ludvig Hektoen and his associates, under the general editorship of Dr. Morris Fishbein, have compiled and annotated over eight thousand selected references for the National Foundation for Infantile Paralysis. The book is more than a list of papers, for the most important references have been carefully evaluated and a brief summary, usually less than six lines in length, gives the essential material contained in the article, sometimes disclosing facts that are not implied in the title of the paper. It is this aspect of the bibliography that makes the book of particular importance to the medical profession.

Beginning with the paper by Underwood in 1789, the bibliography continues through the year 1944. There are a full index of authors and a subject index giving references to the many aspects of poliomyelitis that have been investigated in the past. Thus, one can readily find out the most significant references to such subjects as facial-nerve paralysis in poliomyelitis, flies as carriers of the disease, seasonal incidence, the cerebellar form of poliomyelitis, the involvement of the cerebrospinal fluid, chronic anterior poliomyelitis, quarantine, Theiler's virus and the relation of tonsillectomy to poliomyelitis.

The book is a good example of co-operative research by a chief editor and a fully qualified medical reference librarian. It can be recommended without question as a standard work. The volume is singularly free from error, usually complete and clearly printed, with two indexes that are among the best that have ever been assembled. The editor and the compiler are to be congratulated on the publication of an outstanding work on infantile paralysis.

NOTICES

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, February 7, 194

Arrangements will be made, so far as is possible, for candidates to take the Part I examination (written paper and submission of case records) at places convenient for them. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held June 1–7, 1947, at Pittsburgh. Notice of the exact time and place of the Part I and Part II examinations will be sent to all candidates well in advance of the examination date.

For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

PUBLIC-HEALTH FELLOWSHIPS FOR PHYSICIANS AND ENGINEERS

Announcement is made by Surgeon General Thomas Parran of the United States Public Health Service that applications for fellowships in postgraduate public-health training for physicians and engineers for the school year beginning in the fall of 1947 will be received at any time prior to May 1, 194

The fellowships are made possible by a grant of $228,4 from the National Foundation for Infantile Paralysis through funds contributed to its "March of Dimes." Fifty-three students were awarded fellowships for the school year beginning in September, 1946.

The fellowships provide graduate training of approximately nine months in an accredited school of public health or an acceptable school of sanitary engineering, followed by three months of field training, and are open to men and women citizens of the United States, under forty-five years of age. Physician applicants must have completed at least a year's internship. Engineering graduates with a Bachelor's or higher degree in sanitary, civil or chemical engineering are eligible; and those with other engineering degrees who have had experience in the public-health or sanitary engineering field may also submit applications.

The specific purpose of the fellowships is to aid in the recruitment of trained health officers, directors of special services and engineers to help fill hundreds of vacancies existing in state and local health departments throughout the country. The fellowships are intended for newcomers to the public health field and are not open to employees of state and local health departments, for whom federal grant-in-aid funds are already available to the states.

Applicants for fellowships may secure further details by writing to the Surgeon General, United States Public Health Service, 19th and Constitution Avenue, N. W., Washington 25, D. C., Attention: Public Health Training.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 9

FRIDAY, JANUARY 10

*9:00-10.00 a.m. Sterility. Dr. Somers Sturgis. Joseph H. Pratt Diagnostic Hospital.

*10.00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

12:00 m.–1:00 p.m. Clinicopathological Conference. (Boston Floating Hospital.) Joseph H. Pratt Diagnostic Hospital.

(Notices continued on page xv)

NOTICES (*Continued from page 44*)

MONDAY, JANUARY 13
*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, JANUARY 14
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
8:00 p.m. Harvard Medical Society. Amphitheater, Peter Bent Brigham Hospital.

WEDNESDAY, JANUARY 15
*9:00–10:00 a.m. Rheumatic Fever. Dr. T. Duckett Jones. Joseph H. Pratt Diagnostic Hospital.
*11:00 a.m.–12:00 m. Medical Clinic. Amphitheater. Children's Hospital.
*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

OCTOBER 11–MAY 14. Metropolitan State Hospital. Page 398, issue of September 12.

JANUARY 7. Greater Boston Medical Society. Page 956, issue of December 26.

JANUARY 9. Recent Advances in Surgery. Dr. Fiorindo A. Simeone. Nantucket Association of Physicians. 8:30 p.m. Haverhill.

FEBRUARY 7. American Board of Obstetrics and Gynecology. Page 44.

FEBRUARY 9. National Conference on Medical Service. Page 956, issue of December 26.

APRIL 28–MAY 2. American College of Physicians. Page 206, issue of August 8.

MAY 20–22. Massachusetts Medical Society. Annual meeting. Hotel Statler, Boston.

JUNE 9–13. American Medical Association. Page 698, issue of November 7.

JUNE 30–JULY 3. American Urological Association. Hotel Statler, Buffalo.

SEPTEMBER 8–12. American Congress on Obstetrics and Gynecology. Page 636, issue of October 24.

DISTRICT MEDICAL SOCIETY

PLYMOUTH

JANUARY 16. Brockton Hospital, Brockton.
FEBRUARY 20. Moore Hospital, Brockton.
MARCH 20. Goddard Hospital, Brockton.
APRIL 17. State Farm, Bridgewater.
MAY 15. Lakeville Sanatorium, Lakeville.

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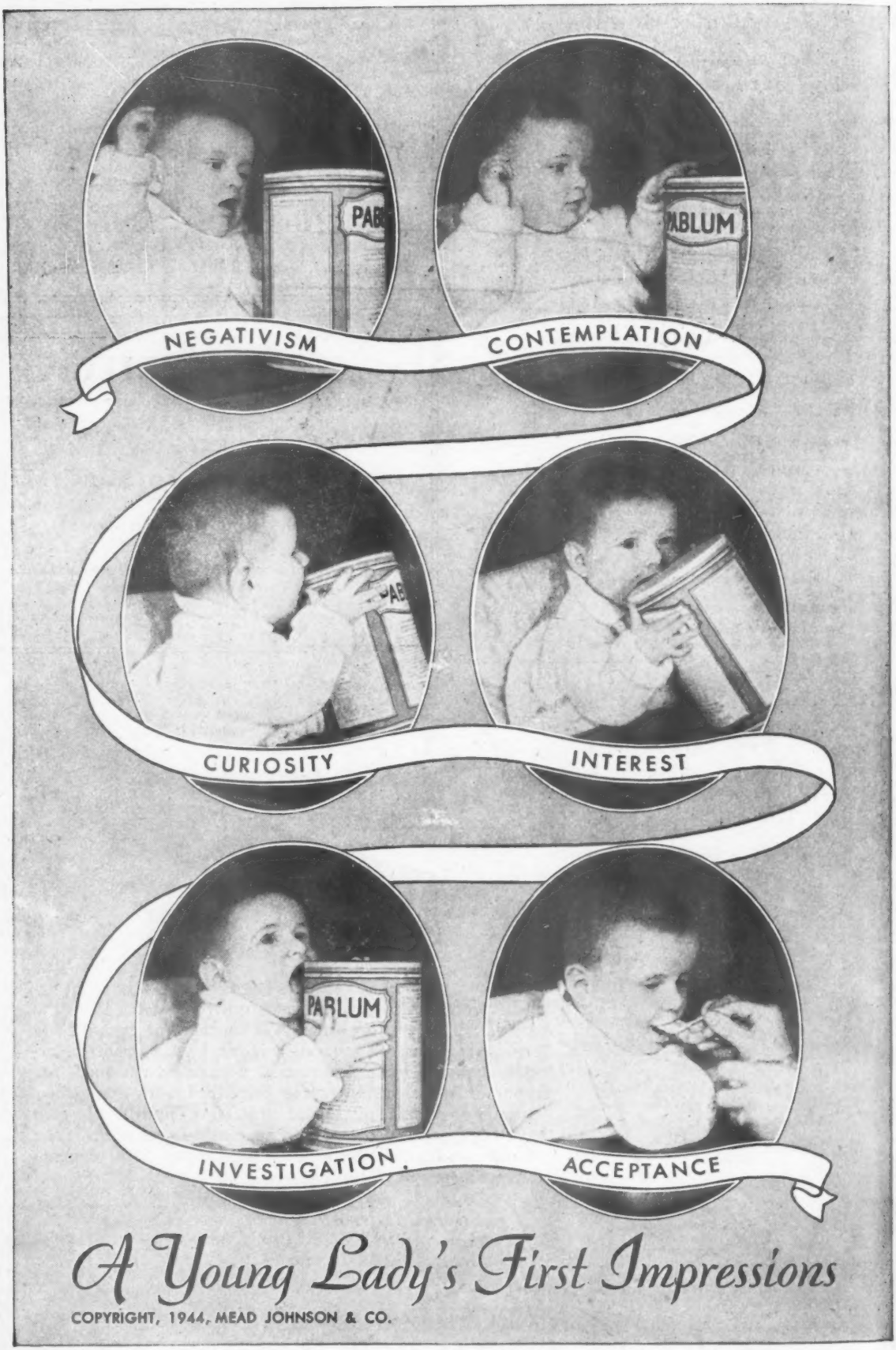
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